An Investigation Of Social Cognition Using Psilocybin and MDMA

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AN INVESTIGATION OF SOCIAL COGNITION USING PSILOCYBIN AND MDMA

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Abstract

Impairments of social function are increasingly thought to be fundamental to the psychopathology of psychiatric disorders. Current treatments are not assessed against these social domains and the effects of medication are poorly understood. Furthermore, the neural mechanisms and psychopharmacology underlying these functions in the healthy population are poorly understood.

This thesis addresses this knowledge gap. A meta-analysis of antipsychotic treatment effects on emotion processing in schizophrenia confirms the lack of efficacy of current treatments in treating these social deficits. Following this, the thesis largely focuses on social decision-making, investigating tasks which model trust, cooperation and social norm violations. A meta-analysis of neuroimaging studies investigating the Ultimatum Game (UG) provides robust evidence of regions underlying the processing of social norms.

Results are presented from two psychopharmacological studies, utilising serotonergic agonists to investigate their effects on social decision-making and emotion processing. The first study administered psilocybin with an open-label design. This study additionally investigated the efficacy of a src-kinase inhibitor to attenuate any psilocybin effect; this followed a placebo-controlled, double-blind design. The second study investigated 3,4-methylenedioxymethamphetamine (MDMA) with a placebo-controlled, double-blind design. Both MDMA and psilocybin caused a decrease in rejection of unfair offers in the UG. MDMA increased cooperation with trustworthy, but not untrustworthy, partners in an iterated Prisoner's Dilemma (PD), as well as

reducing recognition of negative facial affect. Increased cooperation in the PD was accompanied by increased activation in the superior temporal sulcus, cingulate cortex and insula, during feedback of other player's decisions.

The findings of these studies suggest that serotonergic mechanisms are fundamental to the processing of normative behaviour during interpersonal interactions. Manipulation of this neurotransmitter system produced context-sensitive changes in behaviour. These behavioural alterations were accompanied by changes in activity of brain regions proposed to be involved in the processing and appraisal of other's intentions and motivations. It is hypothesised that this was largely achieved through activity at the serotonin 2A receptor. These findings provide insight for the development of new treatment mechanisms for disorders of social cognition.

Acknowledgments

My supervisors, Mitul Mehta and Matthew Kempton, have been a great source of inspiration, guidance, and light-hearted relief over the course of my PhD. I cannot thank them enough. Matthew successfully got me hooked on the statistics underlying meta-analyses, providing a gateway to stats obsession I hadn't realised was possible. I'm grateful to Mitul for giving me the freedom to develop this PhD, and for letting me find and follow my scientific interests. Beyond the rigorous training they have provided, I think the most valuable lesson my supervisors have taught me is that no matter how much pressure or stress there is there's rarely a reason not to laugh your way through it.

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Last but not least, my parents. For everything, thank you.

Declaration of work

This thesis presents two meta-analyses and data collected from two separate experimental studies, as well as two test-retest task validation studies. The meta-analyses presented are my own work, including the literature review and analysis. The study reported in Chapter 3 was initially conceived of and designed by Professor Mitul Mehta and Professor David Nutt (Imperial College London). I designed the social decision-making task completed after the scanning session of this study with the aid of Alex Popescu, paradigm developer at the Centre for Neuroimaging Sciences, KCL. The study reported in Chapter 4 was conceived of and designed by me, in collaboration with my supervisor, Dr Mitul Mehta. The social decision-making tasks used in this study were again designed by me, with the aid of Alex Popescu. For all studies presented in this thesis, I was solely responsible for participant recruitment, data collection and data analysis.

The pre-processing and de-noising steps of the multi-echo resting-state MRI data described in Chapter 3, Section 3.4.4.4 were carried out by Dr Ottavia Dipasquale (Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London). All other data analyses were my own work.

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List of abbreviations

5-HT	Serotonin
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ALE	Activation likelihood estimation
aMCC	Anterior midcingulate cortex
ASD	Autism spectrum disorders
ATD	Acute trytophan depletion
BOLD	Blood-oxygen-level dependent
BPD	Borderline personality disorder
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
ES-SDM	Effect-sized signed differential mapping
fMRI	Functional magnetic resonance imaging
FP	First person
GCPR	G-coupled protein receptors
GS	Games server
HC	Hallucinogenic compound
ICC	Intraclass correlation coefficient
MDD	Major depression disorder
MDMA	3,4-methylenedioxy-methamphetamine
MET	Multifaceted empathy test
NA	Noradrenaline
NHC	Non-hallucinogenic compound
OFC	Orbital frontal cortex

PANSS	Positive and negative symptom scale
PD	Prisoner's dilemma
PFC	Prefrontal cortex
PGG	Public goods game
SANS	Scale for the assessment of negative symptoms
SAPS	Scale for the assessment of positive symptoms
SMA	Supplementary motor area
SRQ	Social reward questionnaire
SSRI	Selective serotonin reuptake inhibitor
STS	Superior temporal sulcus
SVO	Social value orientation
TG	Trust game
TP	Third party
UG	Ultimatum game

Chapter 1 Introduction

1.1 Overview

This chapter will begin with a brief introduction to social cognition and some of the cognitive mechanisms which fall under this umbrella term. It will then move on to discuss how alterations in social cognition appear to be a hallmark of a wide number of psychiatric illnesses. Following this I will present data from a meta-analysis of antipsychotic treatment effects on facial affect processing, highlighting the lack of efficacy in managing social cognitive deficits in schizophrenia[1].

Having identified the need for a more complete understanding of how the brain processes social information, I will then introduce in detail the social decision-making field, the emphasis of this thesis. A review of the current state of knowledge of the psychopharmacology of social cognition will then precede an introduction to the compounds used in the studies that make up the majority of this thesis, followed by a statement of the aims and hypotheses of these studies.

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[1] This section will include work published in the Journal of Psychopharmacology: Gabay AS, Kempton MJ, Mehta MA (2015) Facial affect processing deficits in schizophrenia: a meta-analysis of antipsychotic treatment effects. *J Psychopharmacol* vol. 29 (2) 224-229.

1.2 Introduction to social cognition

Humans have evolved a collection of mechanisms which enable us to navigate a highly complex, social world. Every day we interact with others and with each interaction rely on these cognitive mechanisms. They enable us to recognise the other as an 'other', to infer their thoughts and beliefs, recognise the emotions they may be feeling, and perhaps put ourselves in their shoes and feel what they feel. Many interactions involve a level of trust, be it mundane or deeply personal; and we often rely on others' cooperation to achieve shared goals, and work on an assumption that people will comply with basic social norms. These abstract concepts of trust, cooperation and fairness also implicitly involve the understanding of others' expectations, intentions and motivations. Collectively these mechanisms have become known as 'social cognition', and it has been argued that social pressures resulting from increasing group sizes partly contributed to both primate evolution and the evolutionary development of the human neocortex (Brothers, 2002; Dunbar, 2003).

Social cognition includes a number of low-level processes which are by-and-large not restricted to human cognition, as well as higher level processes (Adolphs, 2009; Gertz et al., 2016; Parr et al., 2005; Parr, 2011; Puce and Perrett, 2003; Watson and Platt, 2012). The low level processes include distinguishing biological from non-biological motion, aspects of social judgement, and facial affect recognition. Experiments investigating the ability to distinguish different types of motion use point-light animations of, for example, people moving; neural correlates of viewing these images are compared to viewing random point-light movements or an inverted human-like animation

(e.g. Grossman et al., 2005; Puce and Perrett, 2003; Saygin et al., 2010). In addition to some higher level processes, which will be discussed in detail later in this chapter, of these low level processes this thesis is concerned with facial affect recognition. Charles Darwin conducted a simple, single-blind experiment of emotion recognition, published as part of his 1872 book, 'The Expression of the Emotions in Man and Animals' (Darwin, 1872). From this he posited that there are a set of universal emotions, recognisable from the facial expressions of those experiencing them (Snyder et al., 2010). Building on this work a number of decades later, Paul Ekman demonstrated that six core emotional expressions were recognisable across cultures: sadness, fear, anger, happy, disgust and surprise (Ekman et al., 1969). This work precipitated a wealth of research into facial affect recognition. While this model of six universal emotions has been questioned, the premise of some universality across cultures is not challenged (e.g. Jack et al., 2016, 2012). Recognition of other's emotional expression plays a key role in successful interpersonal interactions, facilitating aspects of other social cognitive skills such as empathy and theory of mind (more on these below). A large meta-analysis of functional magnetic resonance imaging (fMRI) studies identified a network of brain regions involved in facial affect recognition, including limbic and insular regions (Fusar-Poli et al., 2009).

The ability to correctly identify the emotion being expressed by another individual is clearly important to social interactions. Equally, being able to consider the thoughts and intentions of another individual as being different from one's own plays an essential role. Theory of mind (ToM) is the ability to infer the beliefs, emotions and intentions of another agent, to have a

representation of an other's thoughts; it is an ability which typically developing humans are able to display from age four or five (Baron-Cohen et al., 1985; Premack and Woodruff, 1978; Wimmer and Perner, 1983). It is a central mechanism on which much social interaction relies, enabling one to track others' points of view, beliefs and false beliefs, as well as being a key ability for both cooperation and deception (Frith and Frith, 2012). ToM has been described as having a cognitive and affective component, with inferring complex emotional states being reliant on the affective component while representation of someone's false-beliefs being an example of the cognitive component (Bodden et al., 2013; Molenberghs et al., 2016).

A recent meta-analysis of 127 neuroimaging studies revealed a core network of regions which are consistently activated during both cognitive and affective ToM tasks. These included areas of the medial prefrontal cortex, bilateral temporal-parietal junction, precuneus and the middle temporal gyrus (Molenberghs et al., 2016; Schurz et al., 2014).

The affective component of ToM has been equated with the *cognitive* component of empathy (Walter, 2012). Empathy is a construct of which there are numerous proposed definitions (Bernhardt and Singer, 2012). Chief among the themes which empathy covers is the idea of experiencing the emotions which another individual may be feeling. This involves being able to identify and understand the emotional content of the other's experience, which can be considered equivalent to affective ToM, and is termed cognitive empathy (Walter, 2012). Importantly, cognitive empathy does not necessarily evoke the same feelings in the individual. Affective empathy *does* evoke these feelings,

providing not only an understanding of how someone else feels, but viscerally experiencing those same emotions. Meta-analyses of empathy studies have identified a core network of brain regions involved in empathic response. Key among these are the dorsal anterior and mid-cingulate cortex, anterior insula, and supplementary motor area (Fan et al., 2011).

Social interactions often require a balance between emotional and 'rational' cognitive motivations, sometimes referred to as hot and cold cognition (Kluwe-Schiavon et al., 2016; Roiser et al., 2009; Zimmerman et al., 2016). The ability to resolve these conflicting, social motivations may have become a key factor in evolutionary fitness. The conflict between emotional, social and cognitive motivation has been studied using social decision-making tasks (Rilling and Sanfey, 2011; Stallen and Sanfey, 2013). Social decision-making tasks are an important model of the interplay between social and emotional cognition and reasoned, self-interest judgments, as well as illuminating how trust and cooperation play a role in our interactions with one another. These tasks are believed to involve psychological processes key to effective functioning.

The social decision-making field uses a number of tasks adapted from behavioural economics to investigate the influence of social pressures on decision-making. These include the Trust Game, Ultimatum Game, Prisoner's Dilemma, Public Goods Game and the Dictator Game (Rilling and Sanfey, 2011). In each of these games, the 'rational', optimal strategy for the player is to maximise their individual pay-off, but participants are routinely seen to play non-optimal strategies (Camerer, 2003; Güth et al., 1982). Social decision-making,

including alterations seen in psychiatric illness, will be discussed in greater depth in Section 1.5.

1.3 Social cognition deficits in psychiatric illness

For many people deficits in social cognition are epitomised by autism spectrum disorders (ASD). What is less appreciated in the general population is that social cognition deficits are a hallmark of a number of psychiatric disorders. ASD, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), borderline personality disorder, and psychotic disorders such as schizophrenia and bipolar have all had social cognitive deficits identified as key components of their presentation and have attracted considerable research attention (e.g. Baron-Cohen et al., 1985; Collin et al., 2013; Dziobek et al., 2011; Kupferberg et al., 2016; Nuechterlein et al., 2004).

ToM deficits have repeatedly been shown in ASD (e.g. Baron-Cohen et al., 1985; Begeer et al., 2012; Li et al., 2010; Peterson, 2014). A number of tasks are used to investigate these deficits. False-belief tasks require participants to correctly predict what an actor believes about a situation when that belief is different from the knowledge of the participant themselves (Wimmer and Perner, 1983). Happé's Strange Stories task requires participants to explain why characters in a story say something which is not literally true (Happé, 1994). The Reading the Mind in the Eyes task (RMET) asks participants to infer mental states from pictures just of someone's eyes (Baron-Cohen et al., 1997). What these and other ToM tasks have in common is the requirement that

individuals understand that other agents have different beliefs, thoughts, emotions and intentions to themselves.

These deficits are not unique to ASD. A recent meta-analysis of 34 studies showed a robust ToM impairment in bipolar disorder compared to healthy controls, with a moderate effect size (Cohen's *d* = 0.63; Bora et al., 2016). A meta-analysis examining ToM deficits in ADHD and ASD found a small impairment in ADHD (Cohen's *d* = 0.45), although it should be noted that this effect was almost entirely driven by studies looking at children rather than adults (Cohen's *d* = 0.56 and 0.04, respectively; Bora and Pantelis, 2016). When comparing these deficits to ASD, the authors found ASD deficits to be much larger than ADHD (Cohen's *d* = 0.77), but it is clear that ToM deficits are present in ADHD. Furthermore, a meta-analysis of ToM impairments in MDD in 18 studies also found a moderate effect size (Cohen's *d* = 0.58), and that ToM impairments were significantly related to severity of depressive symptoms (Bora and Berk, 2016). Finally, a recent meta-analysis comparing ToM in ASD to schizophrenia patients found a very similar level of deficit in both conditions (Bliksted et al., 2016). The studies included in this analysis looked at the false attribution of intentionality to non-biological animations, so differs to those used in the other analyses described here. However, a meta-analysis of ToM in first-episode psychosis and ultra-high risk for psychosis found a large impairment (Cohen's *d* = 1.0) and small impairment (Cohen's *d* = 0.45) respectively, looking at studies using tasks more similar to the other analyses discussed above (Bora and Pantelis, 2016). In summary, it is clear that ToM deficits exist in a range of disorders, with the largest deficits seen in psychosis.

Changes in empathic response have also been seen in a number of psychiatric conditions. A meta-analysis of 37 studies showed that schizophrenia patients score lower than healthy controls in affective empathy tasks, with an effect size of g = 0.36 (Hedge's g is equivalent to Cohen's d, with an added correction for small sample size). Studies have found cognitive empathy deficits in Asperger's syndrome and ASD, and affective empathy deficits specific to emotions of negative valence in ASD (Dziobek et al., 2008; Mazza et al., 2014). Both affective and cognitive empathy deficits were seen in borderline personality disorder (Dziobek et al., 2011). It is interesting that while a number of conditions show alterations in empathic response, the nature of these differ across conditions. This could be a sign of the difficulty in defining empathy (Bernhardt and Singer, 2012), a difference in the illness-specific mechanisms underlying the deficits, or both.

Facial affect recognition deficits have also been demonstrated in a number of psychiatric conditions. Meta-analyses of MDD, ADHD and ASD have all found deficits in patients compared to healthy controls (Bora and Pantelis, 2016; Dalili et al., 2015; Lozier et al., 2014). Dalili et al. (2015) provided evidence for a deficit of recognising five of the six 'basic' emotions (happy, anger, fear, surprise, disgust; Hedge's g range: -0.17 to -0.42), but not for the recognition of sadness, in patients with MDD. Bora and Pantelis (2016) demonstrate a small deficit in the recognition of emotions in ADHD, with the strongest deficits being for anger and fear. Anger, fear and surprise were shown by Lozier et al. (2014) to have reduced recognition in ASD. Schizophrenia shows the most pronounced emotion recognition deficits. Two meta-analyses found large deficits in facial

affect recognition in schizophrenia (Kohler et al., 2010; Savla et al., 2013). Kohler et al. (2010) reported a Cohen's *d* of 0.89, while Savla and colleages (2013) reported a Hedge's *g* of 0.89. These meta-analyses included both medicated and unmedicated patients. Kohler et al. (2010) additionally reported that when restricted to unmedicated patients the effect size rose to 1.41.

Having established the prevalence of social cognition deficits across psychiatric illness, the next section will address the efficacy of medication in treating one of these deficits; that of facial affect recognition in schizophrenia. Schizophrenia is a condition which has been treated pharmacologically for decades (Insel, 2010). As such, there is the potential for many studies relating to treatment outcome. While antipsychotic medication has a clear effect on the positive symptoms, there is little or no effect on cognitive processes (Vingerhoets et al., 2013). The effect of antipsychotic medication on social processing has not been quantitatively assessed. When choosing a domain of social cognition to investigate with regards treatment effects, it soon became clear that facial affect processing had the largest number of studies eligible for such an analysis. Furthermore, as described above, research has shown a large effect size for deficits in facial affect recognition in schizophrenia.

1.4 Treatment of social cognitive deficits (meta-analysis)

This section includes work published in the Journal of Psychopharmacology: Gabay AS, Kempton MJ, Mehta MA (2015) Facial affect processing deficits in schizophrenia: a meta-analysis of antipsychotic treatment effects. *J Psychopharmacol* vol. 29 (2) 224-229.

1.4.1 Abstract of meta-analysis

Social cognition, including emotion processing, is a recognised deficit observed in patients with schizophrenia. It is one cognitive domain which has been emphasised as requiring further investigation, with the efficacy of antipsychotic treatment on this deficit remaining unclear. Nine studies met our criteria for entry into a meta-analysis of the effects of medication on facial affect processing, including data from 1162 patients and six antipsychotics. Overall we found a small, positive effect (Hedge's g = 0.13, 95% CI 0.05 to 0.21, p = 0.002). In a subgroup analysis this was statistically significant for atypical, but not typical, antipsychotics. It should be noted that the pooled sample size of the typical subgroup was significantly lower than the atypical. Meta-regression analyses revealed that age, gender and changes in symptom severity were not moderating factors. For the small, positive effect on facial affect processing, the *clinical* significance is questionable in terms of treating deficits in emotion identification in schizophrenia. We show that antipsychotic medications are poor at improving facial affect processing compared to reducing symptoms. This highlights the need for further investigation into the neuropharmacological

mechanisms associated with accurate emotion processing, to inform treatment options for these deficits in schizophrenia.

1.4.2 Introduction to meta-analysis

Antipsychotic medication is used to treat positive symptoms in schizophrenia (National Institute for Health and Care Excellence, 2014). However, deficits in social cognition have been shown to be strongly associated with functional outcome (Green et al., 2004), and is one of eight domains identified by the initiative "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS), which require further investigation and treatment strategies (Nuechterlein et al., 2004).

In a review of the literature, Kucharska-Pietura and Mortimer (Kucharska-Pietura and Mortimer, 2013) concluded that antipsychotics are unlikely to facilitate the recovery of social cognition deficits in schizophrenia based on a review of 15 articles. By far the most widely studied aspect of social cognition is emotion processing, which is typically assessed using tasks requiring participants to perceive, identify and discriminate between facial emotion expressions. A deficit in these abilities has consistently been found in schizophrenia (Kohler et al., 2010; Savla et al., 2013). In a review specific to the facial affect recognition literature, Hempel et al. concluded, based on eight studies, that antipsychotic medication does not successfully treat this aspect of schizophrenia (Hempel et al., 2010).

While these reviews provide valuable descriptions of the relevant literature, they are unable to provide a quantitative analysis of the effects of antipsychotic medication on these cognitive deficits. It also remains possible that the effects of treatment may be small, or affected by moderating factors such as age, gender or type of medication. In order to address these questions we have performed a meta-analysis of studies specifically investigating the effects of antipsychotics on emotion processing in schizophrenia. For details of the methods, literature search and included studies please see Appendix A.

1.4.3 Results of meta-analysis

1.4.3.1 Overall meta-analysis

The overall pooled Hedge's *g* was 0.13 (95% CI 0.05 – 0.21, *p* = 0.002; see Figure 1-1). Here, a positive effect size represents an improvement in facial affect recognition following treatment. There was no significant overall between-study heterogeneity (*p* = 0.85), and no evidence of publication bias (*p* = 0.49).

1.4.3.2 Subgroup analyses

There was no statistically significant effect when the analysis was restricted to typical antipsychotics (Hedge's *g* = 0.17, 95% CI -0.09 to 0.43, *p* = 0.16). This group showed no significant between-study heterogeneity (*p* = 0.16), and no evidence of publication bias (*p* = 0.95). This analysis included data from 266 participants.

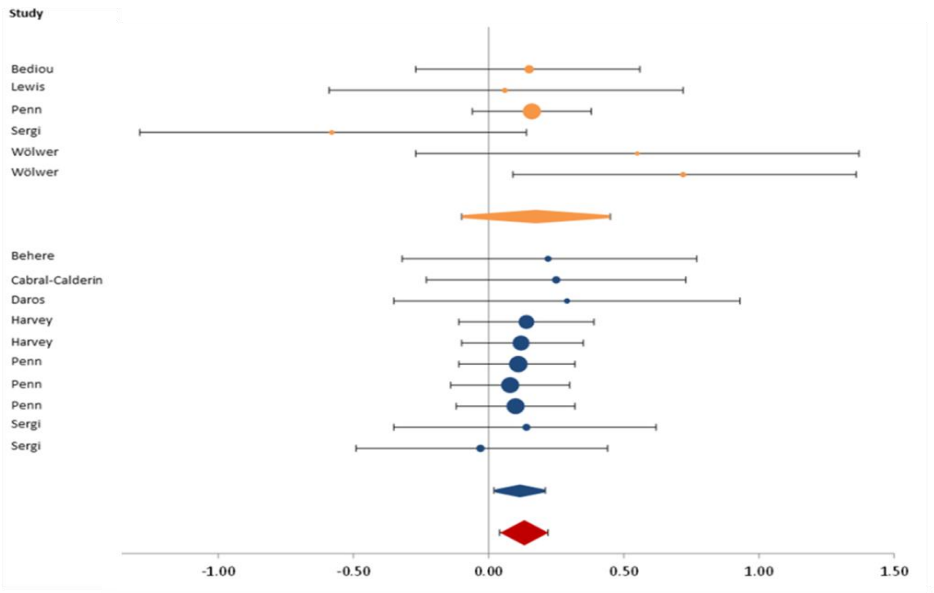
When the analysis was restricted to atypical antipsychotics, the pooled Hedge's *g* was statistically significant, at 0.11 (95% CI 0.02 – 0.21, *p* = 0.01). There was no significant between-study heterogeneity (*p* = 1.0), and no evidence of publication bias (*p* = 0.15). This analysis included data from 896 participants.

1.4.3.3 Meta-regression

We carried out meta-regression analyses to assess the influence of age, gender, duration of treatment, and change in positive and negative symptoms, on the effect size. We were unable to obtain a breakdown of age and gender data across drugs for one study (Penn et al., 2009), and gender data from another (S. Lewis and Garver, 1995). From the nine studies, we were able to obtain pre and post symptom scores from only five, comprising data from 388 patients (the overall effect size for facial affect processing remained significant for this subset of studies, Hedge's *g* = 0.15, p = 0.03). With the exception of one study (n = 26; Bediou et al., 2007), these data came from studies investigating atypical antipsychotics (Behere et al., 2009; Cabral-Calderin et al., 2010a; Daros et al., 2014; Harvey et al., 2006). Four of these five studies reported pre- and post-Positive and Negative Symptom Scale (PANSS) (positive and negative symptom scales) data, while one reported data for the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS). Percentage change in symptom scores were entered into the meta-regression, thus making these two scales comparable.

The meta-regression analyses suggest that neither age nor gender act as a moderator of effect size (*p* = 0.13 and *p* = 0.49, respectively). Furthermore, duration of treatment did not act as a moderator of effect size (*p* = 0.48). In

addition, changes in positive and negative symptoms were not moderators (p = 0.83 and p = 0.97, respectively). That is to say, although these studies did report an improvement in both positive and negative symptoms from baseline to follow-up, the analyses suggest that the observed change in overall effect size for facial affect processing is independent of this symptom change.



Study	Drug	N	Weight (%)	Hedge's g	95% CI
Bediou	Haloperidol	44	3.8	0.15	-0.27, 0.56
Lewis	Haloperidol	18	1.5	0.06	-0.59, 0.72
Penn	Perphenazine	159	13.6	0.16	-0.06, 0.38
Sergi	Haloperidol	13	1.3	-0.58	-0.27, 1.37
Wölwer	Haloperidol	12	1.0	0.55	-0.27, 1.37
Wölwer	Perazine	20	1.6	0.72	0.07, 1.36
	TYPICAL (P = 0.20)	***266***	***22.8***	***0.17***	***-0.09, 0.43***
Behere	Risperidone	25	2.1	0.22	-0.34, 0.77
Cabral-Calderin	Quetiapine	19	1.6	0.25	-0.23, .0.73
Daros	Risperidone	19	1.6	0.29	-0.35, 0.93
Harvey	Quetiapine	124	10.6	0.14	-0.11, 0.39
Harvey	Risperidone	142	12.1	0.12	-0.12, 0.35
Penn	Olanzapine	170	14.5	0.11	-0.11, 0.32
Penn	Quetiapine	161	13.8	0.08	-0.14, 0.30
Penn	Risperidone	161	13.8	0.10	-0.12, 0.32
Sergi	Olanzapine	28	2.8	0.14	-0.35, 0.62
Sergi	Risperidone	32	3.0	-0.03	-0.49, 0.44
	ATYPICAL (P = 0.01)	***896***	***77.2***	***0.11***	***0.02, 0.21***
	OVERALL (P = 0.002)	***1162***	***100.0***	***0.13***	***0.05, 0.21***

Figure 1-1: Forest plot and table displaying results of the meta-analysis. Data identified by study first author and antipsychotic investigated. *X*-axis displays Hedge's *g*. Orange data points are atypical antipsychotics, blue represent typical antipsychotics. The red diamond gives the weighted overall effect size.

1.4.4 Discussion of meta-analysis

We present data from the first meta-analysis of the effects of antipsychotic medication on emotion processing deficits in schizophrenia. We found a small, positive effect on facial affect processing tasks (Hedge's *g* = 0.13). Subgroup analyses suggest that this positive effect is largely driven by atypical rather than typical antipsychotics. However, given the smaller sample size of the typical subgroup, we cannot rule out the possibility that there was not enough statistical power to identify the small effect in this group.

It is important to note that the overall effect size is particularly small. In a meta-analysis of facial affect identification deficits in schizophrenia, Kohler et al. reported a Cohen's *d* of -0.89, rising to -1.41 when restricted to unmedicated patients (Kohler et al., 2010). Thus, it is questionable whether the effect we found in the current analysis would be clinically significant in terms of treating deficits in emotional function. Indeed, a recent multiple-treatments meta-analysis of the efficacy of 15 antipsychotics showed Hedge's *g* ranging from -0.33 to -0.88 (median -0.44) for reducing symptoms compared to placebo (Leucht et al., 2013). It is clear that in comparison, antipsychotic medications are poor at improving facial affect processing deficits. Therefore, it is important to establish the neural mechanisms by which these deficits occur, as well as the small improvements seen with existing treatments, in order to inform better pharmacological targets.

The beneficial effect of antipsychotics on positive symptoms is believed to be due to their antagonistic action at dopamine D2 receptors (Seeman, 2004). It has been argued that dopamine plays an important role in emotion processing

and recognition, and that emotion processing deficits in schizophrenia are associated with altered activity in the amygdala and prefrontal cortex (PFC) (Salgado-Pineda et al., 2005). Evidence suggests that individual differences in performance during processing of emotionally-relevant stimuli are associated with two different polymorphisms related to the dopamine D2 receptor gene (Blasi et al., 2009; Peciña et al., 2013). These are linked to differences in activity in the amygdala, PFC and anterior cingulate cortex. Thus, the dopaminergic effect of antipsychotic medication may play a role in the small changes in facial affect processing seen in the present study.

Stip et al. (Stip et al., 2005) provide data that suggest that treatment with quetiapine improves emotion processing in schizophrenia patients with blunted affect, and that this improvement is associated with modulation of neural activity in the PFC. Conversely, studies using antipsychotic medication in healthy participants have suggested that D2 antagonism impairs facial affect processing (Gibbs et al., 2010; Lawrence et al., 2002), although the medications used in those studies (sulpiride and amisulpride) were not represented in the sample of studies included in the current meta-analysis. These results highlight the subtleties of dopamine D2 receptor involvement in affective processing.

Other mechanisms by which antipsychotics may have an effect on facial effect processing are via serotoninergic action. Serotonin has been implicated as being key to emotion processing in a number of studies (Browning et al., 2007; Chen et al., 2008; Fu et al., 2007; Hornboll et al., 2013). These studies have largely involved administration of selective serotonin reuptake inhibitors (SSRIs) to healthy individuals, as well as in depression studies. The serotonin 2A

receptor (5-HT2A) has particularly been associated with alterations in emotion processing, as shown in studies investigating facial affect processing using ketanserin, a 5-HT2A receptor antagonist (Hornboll et al., 2013; Kometer et al., 2012). Serotonergic action could explain the difference in efficacy between typical and atypical antipsychotics, as many atypicals act on 5-HT2A receptors.

There are surprisingly few pharmacological studies specifically investigating the effects of medication on facial affect processing, and emotion processing as a whole in schizophrenia. As such, the scope of the present analysis is restricted to the nine studies returned by the literature search. However, these studies included a combined total of 1162 patients. It is the nature of meta-analyses that one is limited by the data available, and by the design of the studies included. Some of the included studies used a naturalistic approach to dosage, and only three (Harvey et al., 2006; Penn et al., 2009; Sergi et al., 2007) were double-blind, randomised-control studies. Despite this variability in study design there was no statistically significant heterogeneity seen in the meta-analysis, increasing confidence in its findings. Also, in this meta-analysis all emotional expressions were pooled. Although this may add additional heterogeneity, this was necessary due to the relatively small number of studies available. Ethical and practical considerations limit the use of placebo-controlled studies in patients with schizophrenia and so direct comparisons of medication and placebo within patient groups was not possible. Furthermore, additional analyses investigating how changes in facial affect processing varied with other cognitive processing measures would be useful. However, few of the included studies reported such measures, and for those that did there was inconsistency

in the scales used. Meta-regression analysis assessing the potential modulatory effect of duration of illness may also have been informative. Unfortunately this information was not broken down by medication in a sufficient number of included studies for such an analysis to be carried out. Finally, it should be noted that, as all of the studies used a pre-post design, the effects of learning cannot be ruled out.

1.4.5 Conclusion of meta-analysis

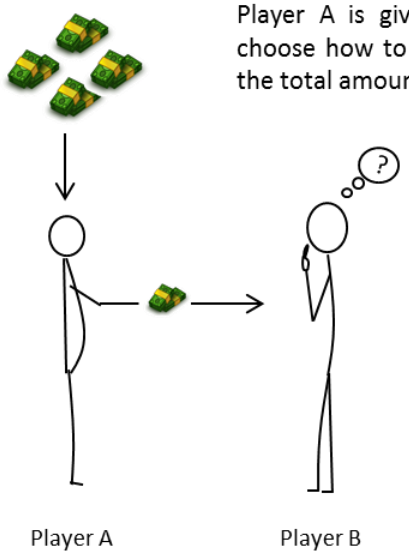
This study presents the first meta-analysis of the effects of antipsychotic medication on facial affect processing. We found a small, positive effect of antipsychotics, substantially lower than both the size of the typical deficit seen in schizophrenia and the efficacy for symptoms reduction, questioning the likely clinical significance. Subgroup analyses suggest the small positive effect is driven by atypical rather than typical antipsychotics, although the difference between the two treatment classes was not significant. Given the small effect size it is important that research continues to investigate the neural and neuropharmacological mechanisms associated with accurate emotion processing, in an attempt to inform further treatment options for these deficits in schizophrenia and other affective disorders.

1.5 Social decision-making

1.5.1 What is social decision-making?

On one hand, social decision-making can be seen as a field of research which attempts to bridge the gap between aspects of social cognition which are generally studied in isolation; such as theory of mind, empathy and emotion processing. Navigating the real-life, complex, social world relies on the interplay of a number of different social cognitive processes, and the field attempts to investigate some of the mechanisms of this interaction. On the other hand, social decision-making can be seen from an evolutionary perspective, attempting to answer the question of how cooperative mechanisms can evolve in a population of individuals for whom self-interest intuitively appears the best strategy. In order to consider the details of the former, it helps to have an appreciation of the latter. The following discussion references a number of tasks used in social decision-making studies. Figure 1-2 summarises these tasks, which can be played as either iterated or single-shot games. A single-shot game is when two players interact only once, while iterated refers to repeated interactions with the same player.

The Ultimatum Game

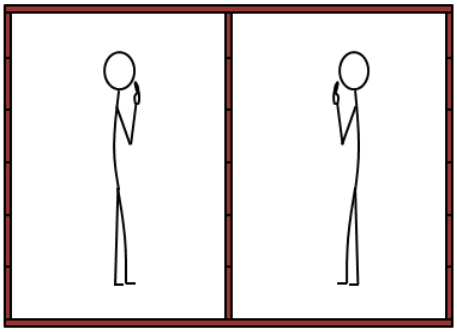


Player A is given an amount of money and asked to choose how to split it with Player B. Both players know the total amount Player A receives.

If player B accepts the offered split, both players receive the money as offered.

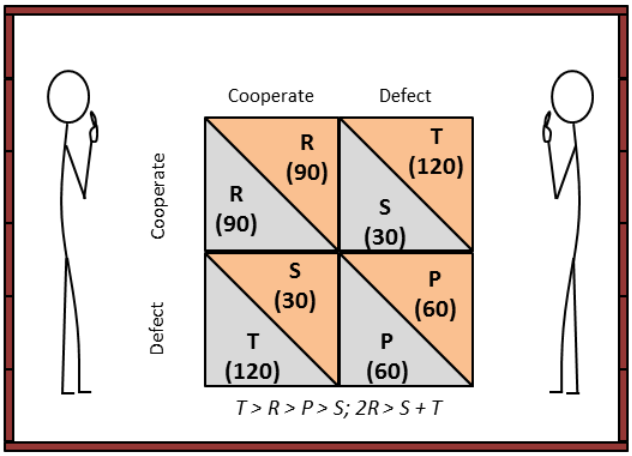
If Player B rejects the offer, neither player receives any money at all.

The Prisoner's Dilemma



Two players are simultaneously asked to choose between cooperating with the other player or defecting.

Each decision is then revealed to the other, and they are awarded points based on the combination of their decisions.



The letters here represent points awarded to each player per combination of responses, with examples given in brackets. A 'true' Prisoner's Dilemma satisfies the condition that T>R>P>S and 2R > S + T.

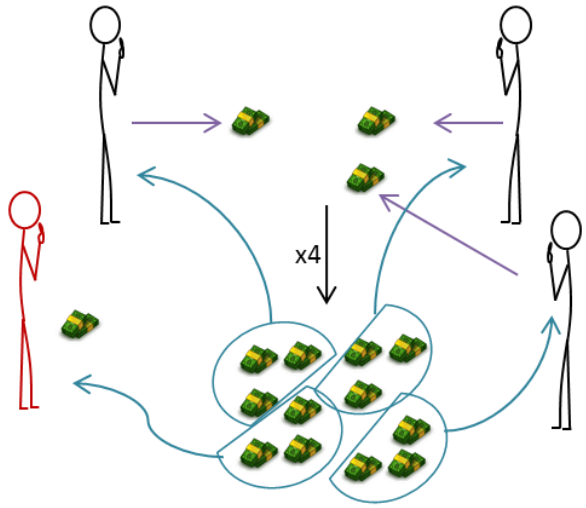
Figure 1-2: Explanation of four commonly used social decision-making tasks (continues on the next page)

The Public Goods Game

Each player is given an equal amount of money at the start of the game. Players simultaneously decide how much to put into the 'public good'. The total amount gets multiplied by a constant and the resulting sum is equally redistributed to all players, regardless of whether they contributed.

In the example on the right, all but the player in red contributed equally to the 'public good'.

After the amount in the middle is multiplied by 4, each player receives an equal share.

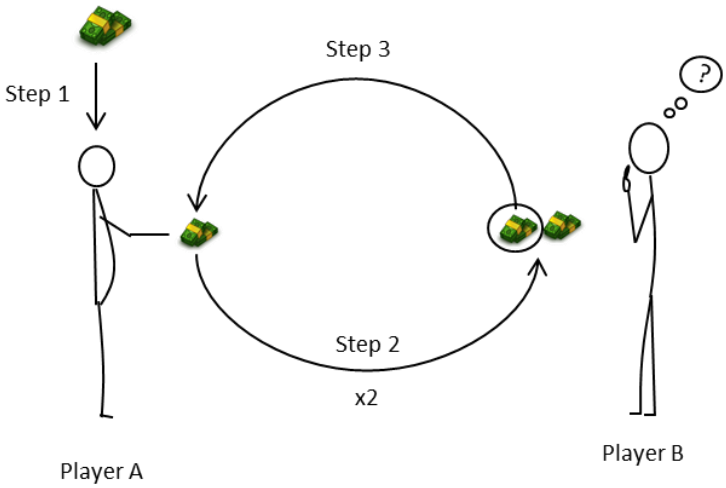


The Trust Game

1. Player A is given an amount of money and decides what proportion (if any) to send to Player B.

2. This amount is multiplied by a constant and given to Player B.

3. Player B then has the opportunity to return a proportion of the amount received.



In the example above, Player A sends all of the money to Player B. This is multiplied by two, and Player B receives this increased amount. Player B then returns half of what was received, meaning that overall, both players end up with equal amounts of money.

Figure 1-2 (continued): Explanation of four commonly used social decision-making tasks (continued from previous page)

Rand and Nowark (2013) provide a simple definition of cooperation as “one individual pay[ing] a cost for another to receive a benefit” (p.413). Social dilemmas occur when “there is tension between what is good for the individual and what is good for the population” (Rand and Nowak, 2013; p. 413). For example, in the classic Public Goods Game (PGG) a group of individuals pay an amount into a public pot. The total contribution of all players is then multiplied by a constant and then redistributed evenly amongst players. There is a clear temptation for each individual to ‘defect’ – pay nothing into the pot and reap the benefits of the other players’ cooperation. Here, the defector would gain at the expense of the group. Typically, players are blind to each other’s decisions, but this can be part of the experimental manipulation. This is a multi-player version of the two-player game, the Prisoner’s Dilemma. In this game players can either cooperate or defect, with each player’s payoff dependant on the combination of decisions. Figure 1-2 shows the payoff matrix for a typical Prisoner’s Dilemma. As an example, both players choosing to cooperate will give them each 90 points. If one player cooperates while the other defects, the cooperative player would receive 30 points, with the non-cooperative player receiving 120 points. Mutual defection gives each player 60 points. It is clear that here, again, the best outcome for all concerned is mutual cooperation, but cooperation opens oneself up to being taken advantage of.

It has been argued that in the absence of the evolution of a ‘cooperative mechanism’, natural selection favours defectors in populations where all individuals are as likely to interact with any other individual (Dreber et al., 2008; Nowak, 2006; Rand and Nowak, 2013). Five such mechanisms have been

proposed, including direct and indirect reciprocity, whereby repeated interactions and reputation effects come into play (Nowak, 2006). An example of direct reciprocity would be if Player A cooperates with Player B in response to Player B having cooperated in the previous round. Indirect reciprocity is when one bases their cooperative behaviour on knowledge of the interacting partner's cooperation with previous partners – this is where reputation comes into play. 'Altruistic punishment' is the costly punishment of another agent's behaviour, and is repeatedly seen in social decision-making tasks (Camerer, 2003; Civai, 2013; Fehr and Fischbacher, 2004; Fehr and Gächter, 2002; Güth et al., 1982; Jordan et al., 2016, 2016; Rand et al., 2013; Sanfey, 2003). It has been argued that the evolution of altruistic punishment can maintain a higher level of cooperation in larger group sizes than in its absence, although it is not considered *necessary* for cooperation (Boyd et al., 2003).

If evolutionary mechanisms have promoted cooperative social behaviour, it follows that there are individual-level mechanisms which lead to these behaviours. The next section reviews the evidence that these behaviours occur, and discusses the tasks used to build this evidence. Following that, I will focus on two specific tasks, the Prisoner's Dilemma and the Ultimatum Game, and consider possible mechanisms underlying these behaviours.

1.5.2 Evidence for cooperation and altruistic punishment

Trust plays a crucial role in almost all social relationships. Trust can be defined as the "willingness to take the social risk of helping another despite the possibility of non-reciprocation" (Rilling and Sanfey, 2011; p. 28). While a

separate concept to cooperation, it undoubtedly underlies decisions to cooperate.

The social decision-making field uses a number of tasks borrowed from behavioural economics. The Trust Game is a task in which one player (the investor) is given a sum of money and is given the option to transfer a proportion to another player (the trustee). Once transferred, the money is multiplied by a constant, and the trustee has the opportunity to return money to the investor. For example, Player A is given £10 and decides to send £5 to Player B. This then gets multiplied by three, meaning Player B receives £15. Player B then has the decision whether to return some of this to Player A. By investing, the investor takes a social risk that the trustee will not return any of the money. The trustee has the opportunity to behave in self-interest, or cooperatively to the benefit of both. The game-theoretical prediction is that in a one-off interaction with a stranger, the trustee should not return any money, and knowing this the investor should choose not to invest any money in the trustee. However, evidence shows that people behave in both trustful (by investing) and trustworthy (by returning) ways in single-shot versions of this game far more frequently than predicted by game theory (e.g. Berg et al., 1995; Camerer, 2003; Espín et al., 2016; Krueger et al., 2007), supporting the idea that trust could be a mechanism underlying humans' propensity to cooperate rather than act in self-interest.

Similarly, in the Pubic Goods Game described in the previous section, the game theoretic 'rational' choice in both a one-off interaction and repeated interactions would be to defect and pay no money into the public pot, thus benefiting from

others' cooperation. However, while there is large variation in how people behave, there is a high rate of cooperation at the beginning of these games (Camerer, 2003; Fehr and Gächter, 2000; Ledyard, 1994). Here, trust that other people will behave cooperatively underlies the decision to cooperate oneself, rather than defect, and perhaps it is due to the erosion of this trust through repeated play that causes these cooperation rates to decrease in finite-length games.

1.5.2.1 The Ultimatum Game

Parts of this section have been published in the journal Neuroscience and Biobehavioural Reviews: Gabay AS, Radua J, Kempton MJ, Mehta MA (2015) The Ultimatum Game and the brain: A meta-analysis of neuroimaging studies. *Neurosci. Biobehav. Rev* 47, 549–558.

The Ultimatum Game (UG) is one of the most frequently used tasks in recent social decision-making studies. In the game one player acts as proposer and another acts as responder. The proposer is given a sum of money and is asked to split this with the responder. The proposer is typically given a range of options as to how to split the sum, but in all cases must offer some, but not all, of the money. The responder can either accept the division of money, in which case both players receive the amount proposed, or they can reject it, in which case neither player receives any money at all.

According to Rational Choice and Expected Utility Theory, a rational responder in the UG should accept any amount offered by the proposer, as this will represent a gain. Knowing this, a rational proposer should offer the lowest

amount allowed by the rules, typically 10% of the total sum (Glimcher et al., 2009). However, evidence shows that people do not behave in this way, with proposers typically offering closer-to-equal amounts, and responders typically rejecting offers they consider to be unfair. Indeed, studies suggest that while people accept fair, or close to fair, offers (40–50%), rejection rates gradually increase as the offer becomes lower (Civai et al., 2012a; C. Corradi-Dell'Acqua et al., 2013; Güth et al., 1982; Oosterbeek et al., 2003; Rilling and Sanfey, 2011). This finding has been found across cultures (Henrich et al., 2005; although see Oosterbeek et al., 2003 for evidence to the contrary) and is interpreted as being a result of social influences on decision-making. This interpretation is supported by the consistent finding that when the same offers are made in a non-social control condition, typically where it is clear the offer has been computer-generated, rejection rates fall close to zero (e.g. Sanfey, 2003). Thus it is suggested that responders are punishing violations of social norms despite the cost incurred to them, which has been argued to be an adaptive mechanism (Boyd et al., 2003; Nowak et al., 2000; Rand et al., 2013). This is an example of altruistic punishment.

It is worth reiterating the behaviour described above. When individuals are offered a low, but non-zero amount of money in the context of the UG – say £1 out of £10 – the majority will reject that offer despite the fact they will never again interact with the proposer. The logic behind such behaviour has been actively debated. The altruist argument suggests that rejection stems from the desire to punish proposers in the hope they will treat others more fairly in the future. Other considerations include punishment stemming from envy, spite,

selfishness, and pure fairness considerations, with disagreement in the literature as to which of these drive rejection behaviour (Bethwaite and Tompkinson, 1996; Forber and Smead, 2014; Kirchsteiger, 1994).

Some attempts have been made to distinguish between rejection-as-emotional-reaction to unfair treatment, and genuine fairness considerations. A series of studies included a third-party (TP) condition (Civai et al., 2010, 2012; Corradi-Dell'Acqua et al., 2013). In this condition Player 1 would make an offer to Player 2 as usual, but instead of Player 2 choosing whether or not to accept the offer, the study participants were asked to make the decision on behalf of Player 2. If the offer was accepted, it would be split as usual between Player 1 and Player 2; if it was rejected, neither Player would receive any money. The participant making the decision does not receive or lose any money, regardless of the decision made. These studies all found that participants would reject low offers, even when they were not directed at themselves. Furthermore, in one of these studies it was found that participants would reject *hyper-fair* offers (80-90%) in the TP condition but not when the offer is directed at the self (Civai et al., 2012a). The results from these studies suggest that rejection behaviour in the UG is due to fairness considerations, yet these only override self-interest up to a point.

Sanfey et al. (2003) were the first to investigate the neural bases of decision-making in the UG. They argue that the decision to forego a financial gain is a response to the negative emotion elicited by unfair treatment. In order to investigate this, neural activity following receipt of unfair offers was contrasted with activity following fair offers. In this study, offers of 30% or below of the total

stake were considered unfair. The authors discussed increased activations seen in the anterior cingulate cortex, anterior insula, and the dorsolateral prefrontal cortex. They suggest that anterior insula activity was predictive of the decision to reject an unfair offer, and argued that this area not only represented the negative emotion associated with unfairness, but also drove the decision to reject unfair offers.

Many neuroimaging studies have followed from this seminal study, investigating variables such as the context of gain or loss (Guo et al., 2013a; Tomasino et al., 2013a), variations across the lifespan (Katia M. Harlé and Sanfey, 2012) and the influence of competition (Halko et al., 2009a) and emotional states (Grecucci et al., 2013; Katia M. Harlé et al., 2012) on UG behaviour.

In 0, I present a quantitative analysis of neuroimaging findings in the UG field.

1.5.2.2 The Prisoner's Dilemma

The Prisoner's Dilemma (PD) has long been studied. In this two-player game, participants are simultaneously asked to cooperate or defect. Points are awarded based on the combination of responses. Figure 1-2 displays the payoff matrix for the game. A true Prisoner's Dilemma obeys the condition that $T > R > P > S$, and that $2R > T + S$ (letters represent points award for different combinations of decision, as explained in Figure 1-2). Therefore it is clear that mutual cooperation is the best outcome for all involved, as the sum of points rewarded for mutual cooperation (2R) is larger than the sum of points of a defect and cooperative decision (T + S); this is true for both repeated, single-shot games, and in iterative games. However, according to rational choice

theory, in both single-shot and finitely-repeated games, mutual defection is the only rational outcome (Andreoni and Miller, 1993; Axelrod and Hamilton, 1981; Colman, 2003; Cooper et al., 1996), as cooperation opens oneself up to being taken advantage of.

Despite mutual defection being the rational choice outcome, in a landmark study by Robert Axelrod it was shown that cooperation cannot only emerge, but flourish (Axelrod and Hamilton, 1981). This is based on the concept of the 'shadow of the future', which states that with increasing probability of players meeting each other again, cooperation becomes beneficial. Axelrod held a computer tournament where programmes employing a range of strategies played iterated PDs. Evidence for the benefit of cooperation comes from the success of the Tit-for-tat (TFT) strategy, which opens with a cooperative decision then repeats the decision of the other player from the previous round.

A large meta-analysis of studies with human participants playing the PD showed that the highest frequency of studies found 30-40% cooperation rates (Sally, 1995; Figure 2 p. 63). This included both single-shot and iterated games. Therefore, not only are cooperative strategies successful when programmed by computer scientists, game theorists, and interested amateurs who have deep knowledge of strategic benefits and pitfalls (as in Axelrod's experiments); they are also seen in participants drawn from the general populace. This is significant because reciprocal cooperation is present in many real-world social interactions, and the PD is believed to be a simplistic, but effective model of these (Axelrod and Hamilton, 1981; Rand and Nowak, 2013; James K. Rilling et al., 2008; Rilling and Sanfey, 2011).

A number of functional neuroimaging studies have investigated the neural mechanisms underlying PD behaviour. A series of studies from Rilling has pointed to a role for the reward system in reciprocal cooperation in both iterated and single-shot paradigms (Rilling et al., 2002, 2004a, 2004b, 2008). When receiving feedback of mutual cooperation, there was increased activity in the orbitofrontal cortex and ventral striatum, as well as somatosensory association cortex. These activations were interpreted as signalling reward to reciprocal cooperation and the emotional response related to it (Rilling et al., 2002). Furthermore, when looking at ventromedial prefrontal cortex as regions of interest, it was found that the BOLD signal of these regions increased in response to reciprocal cooperation, but decreased when participants received feedback of non-reciprocated cooperation (defection of the other player having cooperated oneself; Rilling et al., 2004a). This was interpreted as signalling a prediction error, as is seen in non-human primates in probabilistic reward paradigms. The involvement of these reward-related areas has been corroborated by others (Gradin et al., 2016; Suzuki et al., 2011).

Other regions found during PD paradigms are areas typically found in social cognition tasks, the superior temporal gyrus, temporal-parietal junction, and posterior cingulate gyrus, interpreted as being involved in processing the intentionality of the other player (Rilling et al., 2004; Suzuki et al., 2011). Anterior insula cortex activity has been found in response to unreciprocated cooperation (James K. Rilling et al., 2008) and when contrasting incongruous outcomes compared to congruous ones (Gradin et al., 2016), which could signal a negative emotional response to the outcome.

Finally, increased right dorsolateral prefrontal cortex (DLPFC) activation was found by Suzuki et al. (2011) during the decision phase when participants were playing with mostly defecting opponents compared to mostly cooperating opponents. The authors suggest this is involved in the inhibition of the instinctive urge to cooperate. Left DLPFC activation was seen when Gradin et al. (2016) compared outcomes where one player defected and the other cooperated to those where they both cooperated or defected. Here this activation was interpreted as being involved in emotion regulation following an aversive outcome.

1.5.3 Social decision-making in psychiatric illness

The complexity of social dysfunction in psychiatric illness is coming under greater scrutiny (Kupferberg et al., 2016; Nuechterlein et al., 2004). In line with this, there have been a number of papers published in the last ten years investigating social decision-making in psychiatric populations. In this section I will discuss this literature with respect to the four psychiatric conditions with the most published social decision-making research: major depressive disorder, schizophrenia, borderline personality disorder, and autism spectrum disorders. It will become clear that social decision-making tasks have the potential to elucidate how social processing alterations in psychiatric illness can manifest in ecologically valid interpersonal interactions. The studies discussed below are summarised in Table 1-1.

Table 1-1: Summary of behavioural findings from studies investigating social decision-making in psychiatric conditions. MDD: major depressive disorder; ASD: autism spectrum disorders; UG: ultimatum game; PD: prisoner's dilemma; TG: trust game. [U]Unmedicated sample;[N]Medication status not reported

Condition	Task	Studies	Summary of findings
MDD	UG	Destoop et al 2012; Gradin et al 2014[U]; Harlé et al 2010[U]; Pulcu et al, 2015; Radke et al 2013; Scheele et al 2013; Wang et al 2014	Equal number of studies reporting increased rejection rates as those reporting no change in rejection rate. One study reports reduced rejection rate (but in a non-clinically diagnosed sample).
	PD	Gradin et al 2016[U]; Pulcu et al 2015; McClure et al 2007[U]	Two studies found no changes in cooperation compared to controls. One study found increased defection in currently depressed compared to remitted patients
Schizophrenia	UG	Csukly et al 2011; Wischniewski & Brüne 2011; de la Asuncio 2015	Two studies found decreased rejection of unfair offers compared to controls. One of these also reported increased rejection of fair offers. The third also reported increased rejection of fair offers, but in the absence of changes in response to unfair offer
Borderline personality disorder	TG	Unoka et al 2009; Franzen et al 2011; King-Casas et al 2008	All studies reported reduced trusting behaviour, although one found this was only in response to untrustworthy faces
	UG	Polgár et al 2014	Reported reduced rejection rates
	PD	Saunders et al 2015	Reported reduced cooperative behaviour compared to healthy controls and bipolar disorder patients
ASD	TG	Ewing et al 2015[U]; Chiu et al 2008	No differences in trusting behaviour reported between ASD and typically developing children, although one study suggested differential incorporation of trustworthy appearance
	PD	Downs & Smith 2004[N]; Li et al 2014[N]	One study found no difference in cooperativeness between ASD and typically developing children. The other showed that ASD children did not discriminate based on reputation effects, which typically developing children did

1.5.3.1 Major depressive disorder

The Ultimatum Game

Major depressive disorder (MDD) is associated with a number of social cognitive deficits (Kupferberg et al., 2016). There are many studies investigating social decision-making in MDD, using the Ultimatum Game (UG; Destoop et al., 2012; Gradin et al., 2014; Harlé et al., 2010; Pulcu et al., 2015; Radke et al., 2013; Scheele et al., 2013; Wang et al., 2014), Prisoner's Dilemma (PD; Gradin et al., 2016; Pulcu et al., 2015) and Trust Game (TG; Cáceda et al., 2014). The findings of these studies are difficult to interpret due to their variability, although a recent review concludes that there are significant alterations in these tasks in MDD (Wang et al., 2015).

Three studies have found that MDD patients show increased rejection rates of unfair offers (Radke et al., 2013; Scheele et al., 2013; Wang et al., 2014). Scheele et al. (2013) had inpatients complete the UG soon after admission, and again approximately 40 days later. In addition to finding differences between patients and healthy controls, they found no differences across sessions, nor any difference between treatment responders and non-responders. In this study, there was no difference in fairness ratings of unfair offers between patients and controls, suggesting this was not a factor in the differences in rejection rates. This was not the case for patients in the study by Wang et al., who not only found increased rejection rates of unfair offers, but also reduced fairness judgements of those offers (Wang et al., 2014). Radke et al. found that MDD patients not only rejected more unfair offers, but also hyper-fair offers, possibly suggesting an increased sensitivity to fairness considerations (Radke

et al., 2013). All three of these studies included currently depressed patients on medication at the time of the study. A study investigating unmedicated students with clinically significant symptoms of depression (as assessed by clinical psychologists in the study team) found *decreased* rejection rates of unfair offers (Harlé et al., 2010).

In contrast to the above, other studies have found no difference in rejection rates of unfair offers in MDD (Destoop et al., 2012; Gradin et al., 2014; Pulcu et al., 2015). Gradin et al. did, however, find differences in the neural responses to different offers between healthy controls and MDD patients (Gradin et al., 2014). The authors report that in MDD, the nucleus accumbens and dorsal caudate did not increase activity in line with increasing offer as much as healthy controls, suggesting alterations in processing of reward. While no differences were found in rejection rates between MDD patients and healthy controls, Destroop et al did report higher offers when patients acted as proposers (Destoop et al., 2012). Here, the authors suggested this could be due to an increase in harm avoidance, with rejection being considered a possible harm. It should also be noted that these authors used a two-round design, where participants first responded to an offer, then made an offer to the same player. As the authors note, this may have led to patients rejecting less than they would otherwise, to avoid a rejection of their own offer. These studies also had a mix of medicated and unmedicated patients.

Medication should be very carefully considered when looking at UG results in MDD, as it has been shown that acute SSRI administration can alter UG behaviour by reducing rejection rates of moderately unfair offers (Crockett et al.,

2010; see Section 1.6 for more details). Medications being taken by patients in the studies discussed were not limited to antidepressants, but also included antipsychotics and benzodiazepines. As such, difference in the medications across studies could be a key factor in the heterogeneity of the results found in these studies.

The Prisoner's Dilemma

Two studies found no difference in overall cooperativeness in the Prisoner's Dilemma between MDD patients and healthy controls (Gradin et al., 2016; McClure et al., 2007). McClure et al. investigated a sample of mixed depressive/anxiety disorder patients, and found that while there was no overall difference in cooperativeness, the patient group were more likely to cooperate following co-player cooperation in the previous round. This may suggest that patients were less likely to take advantage of other players. Patients in both of these studies were medication free. Pulcu et al (2015), on the other hand, showed that currently depressed patients defected more than remitted patients.

1.5.3.2 Schizophrenia

The Ultimatum Game

Three studies have found alterations in UG behaviour in schizophrenia patients (Csukly et al., 2011; de la Asuncion et al., 2015; Wischniewski and Brüne, 2011). Two of these studies found decreases in rejection rates of low offers by schizophrenia patients compared to healthy controls (Csukly et al., 2011; Wischniewski and Brüne, 2011). In addition, Csukly et al. (2011) reported *increased* rejection rates of *fair* offers. Wischniewski and Brüne (2011) found

that there was no difference between patients and controls in fairness comprehension in a modified Dictator Game, suggesting that the change in rejection rates in the UG do not reflect differences in the concept of fairness. The increased rejection of fair offers in patients compared to controls was also seen in another study, but in the absence of a statistically significant reduction in unfair offer rejections (de la Asuncion et al., 2015).

Unfortunately these studies did not include a non-social control condition. Such a condition would involve participants being told that the offers are randomly generated by a computer, rather than offers being made by another person. Had such a condition been included in these studies it would be easier to disentangle the processes behind the rejection of fair offers.

1.5.3.3 Borderline personality disorder

The Trust Game

In a study investigating Trust Game (TG) behaviour in borderline personality disorder (BPD), Unoka et al (2009) found reduced investments as Player 1 in the game, compared to both healthy controls and patients with MDD. No difference was seen between MDD and healthy controls. While patients were not medication free, similar medications were taken across patient groups. In this study, there was a control task which was identical to the TG, but rather than the trustee returning money, investors would invest in a random lottery. No differences were seen in this game across groups, suggesting the reduced investment in BPD represented a lower level of trust.

In a repeated TG, BPD patients reduced their investment to untrustworthy trustees displaying angry faces, while healthy controls only did this in response to neutral faces (Franzen et al., 2011). The authors of the study point to the hyper-vigilance of BDP patients to social stimuli, particularly when the stimuli signals threat or rejection (Linehan, 1995; cited by Franzen et al., 2011).

Reduced trusting behaviour of BPD patients was also seen when acting as investors in an earlier study, which paralleled this finding to reduced self-reported interpersonal trust, compared to healthy controls (King-Casas et al., 2008). In this study, patients also played a repeated TG acting as trustees. Using the amount invested in trustees as a measure of ongoing cooperation, these authors report that healthy investors invest similar amounts in both patients and healthy controls in early rounds of the game. However, as the game progressed, cooperation was not maintained with BPD patients, evidenced by a significant decrease in investment compared with controls. Through a thorough exploration of the data, the authors show that while breaches in trust occur in both groups, attempts to repair trust through 'coaxing' – returning all of the money made by the trustee in a round – is seen less frequently in patients than in controls.

King-Casas et al (2008) also showed abnormal processing of violations of social norms in the anterior insula compared to healthy participants. They report that although signal change in an insula region-of-interest tracked the amount returned to the investor in both groups, insula did not show higher activation in response to low investment compared to higher investment in the BPD group as it did in healthy controls. The authors report this as being evidence that low

investments are not considered a norm violation in patients. However, looking at the data behind the breakdown in cooperation, it would appear that BPD patients were more sensitive to the lowest investments, and sanctioned these by low repayments significantly more than healthy trustees. Sanctioning low investments or offers in economic exchange games is often considered norm enforcement, which suggests that, behaviourally at least, patients may be *more* sensitive to norm violations. Despite this, the lack of trust and inability to repair breakdowns in cooperation do suggest some altered social norm processing in BPD.

The Ultimatum Game

Rejection rates of unfair offers in an Ultimatum Game (UG) were found to be less in medicated BPD patients compared to healthy controls (Polgár et al., 2014). Rejection behaviour is considered to be altruistic punishment of social norm violations. This finding supports the interpretation of BPD behaviour in the TG discussed above that BPD patients show altered processing of social norms. The authors of the UG study suggest reduced rejection may be indicative of patients' lower expectation of positive social outcomes.

Furthermore, it was found that the control group rejected more offers when the picture of the proposer displayed a negative facial expression compared to when displaying a positive one. This effect was not seen the BPD group. Unfortunately, the authors of the study did not report any comparison of facial affect recognition across groups in this study; previous research suggests BPD patients have impaired emotion processing (Derks et al., 2016; Meyer and

Morey, 2015). An analysis taking into account the medication of the patient group suggested that responses did not vary with medication.

The Prisoner's Dilemma

One study compared behaviour in an iterated Prisoner's Dilemma (PD) game in borderline personality disorder to healthy controls and euthymic bipolar disorder patients (Saunders et al., 2015). It was found that the proportion of cooperative decisions made by borderline personality disorder patients was less than both healthy controls and bipolar disorder patients. No differences were seen between bipolar disorder and control groups.

Interestingly, the authors report that borderline personality disorder patients cooperated about 50% of the time, no more than chance (Saunders et al., 2015). Borderline personality disorder patients were also less likely to cooperate following a mutually cooperative round than both bipolar disorder patients and healthy controls. Together, these findings are interpreted as showing that borderline personality disorder patients have "…difficulties in establishing and maintaining reciprocally cooperative relationships" (p. 1597).

With the lack of non-social control task it is again difficult to further establish the mechanisms underlying this altered behaviour. However, it does corroborate the findings from the other tasks discussed in this section, that borderline personality disorder shows altered social reciprocity, and that this may be due to a lack of trust, leading to difficulties maintaining cooperative relationships.

1.5.3.4 Autism spectrum disorder

The Trust Game

Ewing et al (2015) sought to investigate how the perception of trustworthiness altered behaviour as investors in a repeated, single-shot Trust Game (TG) in children with autism spectrum disorder (ASD) compared to typically developing controls. By presenting pictures of the other players when participants were deciding how much to invest, the experimenters manipulated how trustworthy they appeared. They found that while overall investor behaviour was similar across groups, children with ASD's investments did not change with trustworthy appearance, while typically developing children's did. However, there was no deficit in rating the trustworthiness of each picture, and furthermore, the ASD group *did* show different investor behaviour based on reputation effects, in line with the findings from the control group. The authors suggest alterations in spontaneous inference of facial features or reduced social interest may be behind these findings.

In a different study, high-functioning ASD adolescents were found to behave no differently to typically developing controls as trustees in a multi-round TG (Chiu et al., 2008). However, with a complex analysis of neuroimaging data captured during the task (the details of which are beyond the scope of this discussion), the authors show that the pattern of activity of the cingulate cortex when making trustee decisions failed to resemble self-specific responses seen in typically developing controls in another, larger dataset.

When considering the behavioural data, it should be noted that the size of the ASD samples were relatively small in both studies discussed here: 12 and nine (Chiu et al., 2008; Ewing et al., 2015, respectively). With that in mind, both of these studies suggest that overall behaviour in the TG is not different in ASD compared to controls, although there may be some difference in consideration of trustworthy appearance.

Prisoner's Dilemma

Two studies have shown that very similar behaviour in the Prisoner's Dilemma (PD) in ASD compared to typically developing children (Downs and Smith, 2004; Li et al., 2014). Downs and Smith (2004) found no differences in cooperative behaviour between these two groups, but did find a difference between both of these groups and children with attention-deficit/hyperactivity disorder. Li et al (2014) found that when typically developing children played an iterated PD with other children they had seen doing 'nice' things previously, they cooperated more than with those children they had seen doing 'naughty' things. This effect was not seen in high-functioning children with ASD, despite their ability to correctly categorise 'naughty' and 'nice' behaviours.

The results of these two studies suggest that on the whole, children with ASD behave similarly to typically developing children in the PD, but may not be able to fully integrate social information into their decision-making process.

1.5.4 Conclusion

The social decision-making field employs a number of tasks to investigate the processes behind complex social interactions. These tasks rely on a number of

social processes and model complex, abstract concepts such as trust, fairness and cooperation. The tasks are increasingly being used to investigate how the well-documented social deficits in psychiatric illnesses may come together to affect behaviour in ecologically valid models of social interactions.

The studies reviewed here show a diverse range of altered behaviour in psychiatric conditions, and describe how these differences can be used to understand the idiosyncrasies of each condition. However, it is clear that while there are certainly hints of disrupted behaviour, more work needs to be done to establish the extent of the deficits and possible mechanisms underlying them. The variation in results described above illustrate that the field as a whole would greatly benefit from a meta-analysis of studies comparing social decision-making in psychiatric populations to healthy controls. If the data permitted, meta-regressions of symptom scores and medication would help to elucidate the contribution of these factors to behaviour. In the next section I will review the psychopharmacological literature to establish what is known about the neurochemical mechanisms underlying social cognition and social decision-making.

1.6 The psychopharmacology of social cognition

As outlined in Section 1.5, research on social decision-making has begun to investigate how healthy individuals may differ from those with psychiatric conditions in terms of their social interactions. It is important that this research continues, in order to clarify the details of the behavioural mechanisms underlying any alterations. It is also of great importance to understand the *biological* mechanisms underlying these behaviours, and the variations seen across people. Investigating these mechanisms in healthy individuals will not only help to establish how the brain encodes such complex concepts as trust and fairness, but will also provide potential treatment targets for people in which alterations of these concepts disrupt their quality of life.

Psychopharmacology provides powerful methods to investigate neural substrates of behaviour. By using pharmacological interventions, it is possible to mimic or block the effects of endogenous neurotransmitters (even limited to specific receptor subtypes), or regulate their availability. In doing so, one can elucidate the contribution of particular neurotransmitter systems and receptor mechanisms to cognition. In this section I will discuss psychopharmacological research looking at social cognition, with a particular emphasis on empathy and social decision-making. The discussion will be limited to those studies investigating these processes in healthy individuals.

Oxytocin is a neuropeptide which has received a great deal of attention over the last decade for its putative effects on social cognition (for reviews, see Cochran et al., 2013; Guastella et al., 2010). Specifically, there is evidence that

intranasal oxytocin administration affects emotion recognition (Cardoso et al., 2014; Kirkpatrick et al., 2014; Marsh et al., 2010), empathy (Bartz et al., 2010; Domes et al., 2007; Hurlemann et al., 2010), and social decision-making (Kosfeld et al., 2005; Zak et al., 2007). However, there are mixed results from studies investigating these effects.

Studies suggest an effect of oxytocin on empathy, but these effects appear to be nuanced, while other studies did not report any affects at all. Bartz et al. (2010), for example, found that oxytocin administration only improved empathic accuracy for those with low social-cognitive competence, as measured by the autism spectrum quotient, a questionnaire assessing autistic traits in healthy individuals. Those with higher competence performed equally well on placebo compared to oxytocin. Hurlemann et al. (2010) reported oxytocin-driven improvements in emotional empathy in men but not women. Indeed, male emotional empathy was increased to the level seen in female participants on placebo. These authors reported no change in cognitive empathy (for a brief discussion of the categorisation of empathy, see Section 1.2). Kuypers et al (2014) found no changes in cognitive or emotional empathy following administration of oxytocin.

A meta-analysis of the social effects of oxytocin found a small improvement in emotion recognition with oxytocin administration (Cohen's d = 0.21; Bakermans-Kranenburg and van IJzendoorn, 2013). This same meta-analysis examined research investigating the effect of oxytocin on trust. It did this in the context of differences between the effects of oxytocin on in-group and out-group trust. In these studies, 'in-group' referred to people whom the participants already knew,

had met, or had received positive descriptions of. The authors report a moderate effect size of increased in-group trust, but a non-statistically significant overall effect size for out-group trust (Cohen's *d* = 0.43 and 0.21, respectively).

Serotonin (5-HT) is a modulatory neurotransmitter whose involvement in social cognition and emotion is supported by the role of selective serotonin reuptake-inhibitors (SSRI) in treating depression and anxiety disorders (Fournier et al., 2010; Hieronymus et al., 2016). A series of studies by Crockett et al have implicated the serotonergic system in social decision-making (Crockett et al., 2008; M. J. Crockett et al., 2010, 2013). Acute tryptophan depletion (ATD) is a method used to temporarily reduce the amount of 5-HT available, by depleting one of its precursor compounds (for a critical review of the method, see Young, 2013). Two studies report that reducing 5-HT availability through ATD leads to increased rejection rates of moderately, but not very unfair offers (30% and 20%, respectively) in the Ultimatum Game (UG) (Crockett et al., 2008; M. J. Crockett et al., 2013). Neither of these studies found a corresponding change in fairness ratings of these offers. Crockett et al (2013) found an increase in neural activity in the dorsal striatum when rejecting these unfair offers following ATD compared to placebo, and that the magnitude of this increase was correlated with the increase in rejection rate. These findings suggest that reward mechanisms may be behind 5-HT's influence on social decision-making. Another study looked at the effect of SSRIs in the UG. Acute treatment with SSRIs will temporarily increase the availability of 5-HT in the synapse by

blocking its reuptake. Crockett et al (2010) found that acute SSRI administration *reduced* rejection rates of 30% offers.

In line with these findings, Emanuele et al (2008) found that participants who accepted unfair offers and those who rejected them differed in their platelet serotonin levels. Those who rejected unfair offers had lower levels than those who accepted unfair offers. In a study of cooperativeness in an iterated Prisoner's Dilemma (PD), Wood et al reported more nuanced effects of 5-HT manipulation (Wood et al., 2006). Here, the authors report that reducing 5-HT availability through ATD reduced the proportions of cooperative responses compared to increasing tryptophan (and therefore 5-HT). However, this effect was only seen on the first day of this crossover design study. Analysing the results in more detail, the authors report that participants in the ATD group on day one significantly increased their cooperativeness on day two, when in the increased tryptophan condition; those with the reverse treatment order maintained a relatively high cooperation rate across visits. This raises the possibility that participants alter behaviour with repeated exposure to the task. However, this may also be characterised as an interaction between treatment and treatment order, such that perhaps serotonin disruption alters learning processes in the task.

Another pharmacological method of manipulating 5-HT availability is the administration of 3,4-methylenedioxy-methamphetamine (MDMA), which is a potent 5-HT releaser (de la Torre et al., 2004). MDMA pharmacology will be discussed in greater detail in Section 1.8. Studies with MDMA have found that it increases emotional, but not cognitive, empathy (Hysek et al., 2013; Kuypers et

al., 2014; Schmid et al., 2014). Furthermore, MDMA has been shown to alter emotion processing, as measured by facial affect recognition (Bedi et al., 2009; Hysek et al., 2013; Kirkpatrick et al., 2014; Schmid et al., 2014). Kirkpatrick et al (2014) found that MDMA increased feelings of sociability, while Hysek et al (2013) reported increased prosocial responses on the social value orientation (SVO) questionnaire in men, but not women. The SVO is a questionnaire-based measure of equality preferences. In a trust game, Kuypers et al (2014) reported no MDMA-associated changes in trust or reciprocity.

Stewart et al (2014) reported an increase rating of trustworthiness of facial stimuli following acute MDMA administration compared to controls. Furthermore, in a Dictator Game, these participants offered more money compared to controls, and compared to their own non-MDMA session. In this game participants offer a proportion of money as in the UG, but the other player is unable to reject it. It is considered a measure of altruism (Rilling and Sanfey, 2011). The authors also found a larger difference between the largest amount offered and lowest amount accepted by the MDMA group in the UG. While these data suggest an MDMA effect on social cognition, it should be noted that this was a naturalistic study – the MDMA taken belonged to the participants, so there was control of dose or purity of the drug.

There is some evidence to suggest that MDMA's effects on rodents are driven by increases in oxytocin (Ramos et al., 2013; Thompson et al., 2007). In humans, however, there are conflicting results in the literature. A number of studies report MDMA-induced increases in plasma oxytocin levels (e.g. Dumont et al., 2009; Hysek et al., 2013; Kuypers et al., 2014; Schmid et al., 2014)

Dumont et al (2009) found that increases in self-report measures of prosociality correlated with increased plasma oxytocin levels following MDMA administration. A recent study investigating the influence of variations in an oxytocin receptor gene found a difference of genotype on self-report measures of sociability while on MDMA (Bershad et al., 2016). Kirkpatrick et al (2014a) reported a correlation between intranasal oxytocin-induced and MDMA-induced subjective reports of increased playfulness and insightfulness; this was seen on low dose, but not a high dose of oxytocin however, leading the authors to acknowledge the possibility that this finding was a false positive.

Kuypers et al (2014) found no correlation between MDMA-induced increases in emotional empathy and plasma oxytocin levels. Similarly, neither Hysek et al (2013), Kirkpatrick et al (2014b) nor Schmid et al (2014) found any correlation between MDMA-induced increases in plasma oxytocin and prosocial effects. It is important to note that there is evidence to suggest that plasma and brain oxytocin levels are not related (Kagerbauer et al., 2013; Martin et al., 2014), so the lack of relationship between prosocial effects and plasma concentrations does not necessarily suggest *central* oxytocin release is not partially responsible the prosocial effects of MDMA. As such, the relationship between MDMA-induced increases in oxytocin and the drug's subjective effects requires clarification.

Taken together, the evidence discussed above suggests a role for 5-HT in social cognition. On the whole, increases in 5-HT levels appear to increase self-report measures of prosociality. In social decision-making, there is an increase in cooperation and altruism, and a decrease in altruistic punishment in the UG.

This latter finding is harder to interpret in the context of prosociality. Crockett et al (2010) interpret it in terms of harm avoidance. In the context of reduced rejection rates being seen following training in mindfulness meditation, it has been interpreted as being a sign of increased cooperation (Kirk et al., 2016), which would fit with the findings in the PD.

While studies investigating oxytocin and serotonin make up the majority of psychopharmacological research in social cognition, other mechanisms have been examined. Testosterone has been shown to increase the proportion of fair offers in the UG (Eisenegger and Naef, 2011), as well as reduce trust, but increase reciprocity, in the trust game (Boksem et al., 2013). Using a selective reuptake-inhibitor, noradrenaline (NA) was found to increase social engagement and cooperation (Tse and Bond, 2002), and enhance recognition of disgusted and happy facial expressions (Harmer et al., 2008). Furthermore, d-amphetamine and methylphenidate, both of which have affinity for NA and dopamine transporters (Han and Gu, 2006), have been shown to alter emotion processing; Wardle and Wit (2012) showed an increased sensitivity to subtle facial expressions with d-amphetamine, and Hysek et al (2014) showed an increase recognition of sad and fearful faces with methylphenidate.

Glutamate and γ-Aminobutyric acid (GABA) are the main excitatory and inhibitory neurotransmitters respectively (Stahl, 2013). Yet there is a lack of psychopharmacological research investigating the direct effects on social cognition of drugs targeting these systems in the healthy, human population. One study of typically developing children and those with ASD used magnetic resonance spectroscopy to investigate the relationship between glutamate,

glutamine and GABA concentrations in the pregenual anterior cingulate gyrus and measures of emotion recognition and social responsiveness (Cochran et al., 2015). They found that glutamine concentrations showed a statistically significant negative correlation with emotion processing, and a positive correlation to social reactivity, but there were no significant relationships with GABA. A candidate gene study found a relationship between self-reported altruism (which is related to processes underlying some social decision-making paradigms), in patients with schizophrenia, and the gene encoding the $GABA_A$ receptor β_2 subunit (Tsang et al., 2013).

The relative lack of evidence for the direct involvement of the glutamatergic and GABAergic neurotransmitter systems in social cognition should not be taken to mean they are not involved. Serotonin, dopamine and noradrenaline are all neuromodulators, meaning they will have indirect effects on other neurotransmitter systems.

With the serotonin system, and its interaction with the oxytocin system, being most strongly implicated in social cognition, these represent good targets to further elucidate the psychopharmacological and neural mechanisms underlying cooperation, trust and fairness considerations in healthy individuals. Section 1.8 will introduce two serotonergic compounds used in the studies whose findings will be reported in 0 and 0 of this thesis. Prior to this, Section 1.7 will briefly introduce the serotonin neurotransmitter system.

1.7 The serotonin system

The serotonin (5-HT) neurotransmitter system is evolutionarily ancient (Hay-Schmidt, 2000). It has been argued that intellectual capacities of higher primates have been subserved by changes in the organisation of the 5-HT system (Raghanti et al., 2008). 5-HT neurons originate in the raphe nuclei and project widely to cortical and sub-cortical regions (see Figure 1-3A; Andrade and Haj-Dahmane, 2013; Hornung, 2003; Stahl, 2013). There are seven main classes of 5-HT receptor, many with further subtypes, allowing for diverse downstream effects of serotonergic activity (Barnes and Sharp, 1999). Figure 1-3B and C is reproduced from Beliveau et al (2017) and shows the distribution of five different 5-HT receptor subtypes across the human brain.

Of particular interest to the current thesis are the 5-HT1A and 5-HT2A receptors, as well as 5-HT transporters (5-HTT). 5-HT1A receptors have been described as having an inhibitory action on target cells through hyperpolarisation and often act as autoreceptors (Hoyer et al., 2002). 5-HT2A receptors act to increase the intracellular concentration of calcium ions, leading to increased neuronal excitation, and are functionally heterogeneous (Aznar and Klein, 2013; Leysen, 2004). In addition to modulating a wide range of cortical and subcortical neurons, they have been linked to modulating the activity of hormones including oxytocin and prolactin (Barnes and Sharp, 1999; Hoyer et al., 2002; Leysen, 2004). Both of these receptor subtypes have also been shown to have downstream effects on cellular microstructure, leading to alterations in synaptic receptor organisation (Aznar and Klein, 2013). 5-HTT are

involved in the reuptake of serotonin from the synapse, and in this way modulates 5-HT availability (Rudnick, 2006).

As described elsewhere in this chapter, the serotonergic system is strongly implicated in different aspects of social cognition, and Aznar and Klein (2013) argue that the 5-HT2A receptor underlies aspects of this through modulation of emotion-based actions, a view that has been supported in subsequent emotion and social processing studies (e.g. Hornboll et al., 2013; Preller et al., 2016; Schmidt et al., 2013). As such, the studies presented in this thesis utilised two serotonergic compounds, 3,4-methylenedioxy-methamphetamine (MDMA) and psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine). These will be introduced in the following section.

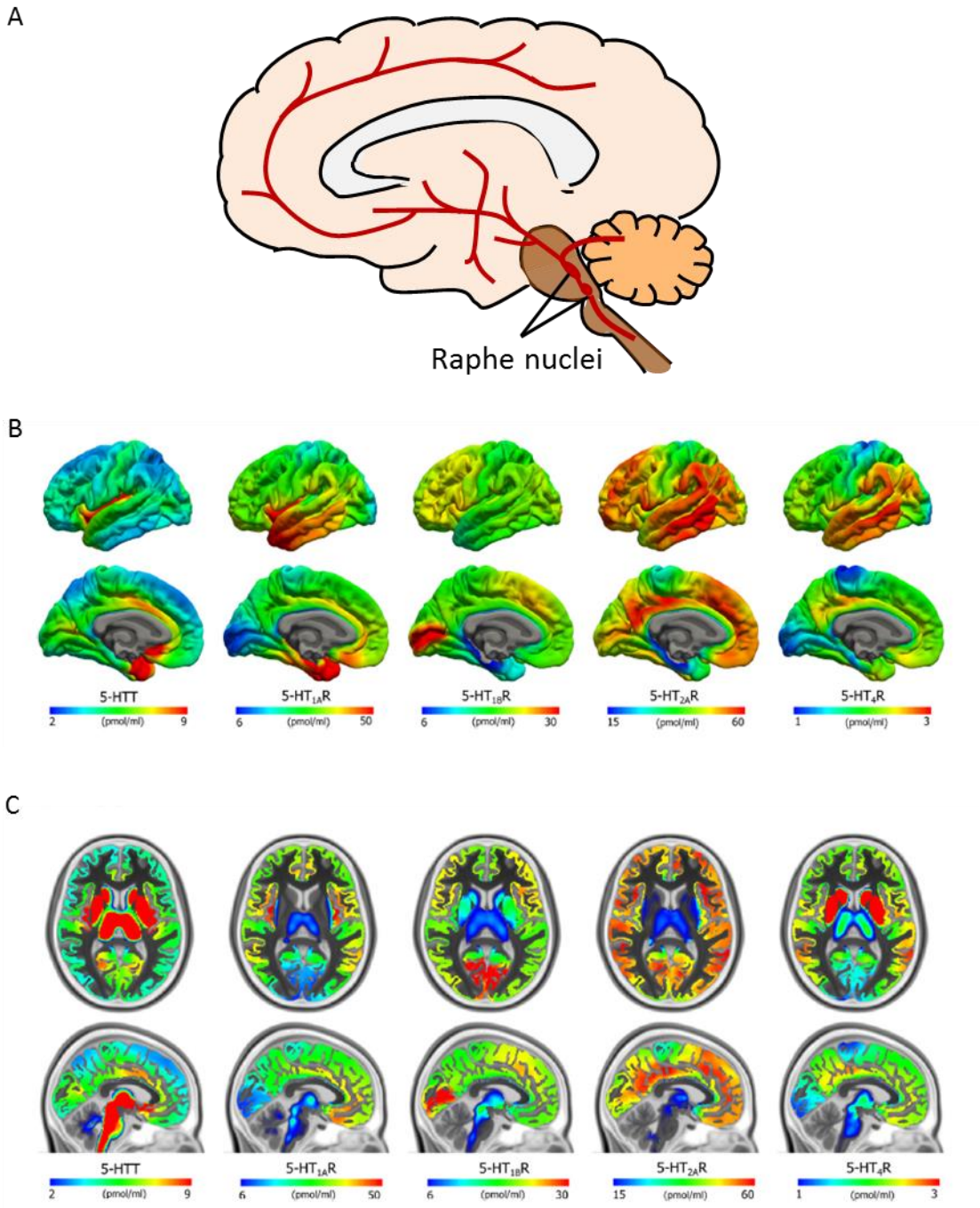


Figure 1-3: A) Diagram showing serotonergic projections from the raphe nuclei to the PFC, striatum, thalamus and other subcortical regions B) Reproduced with permission from Beliveau et al (2017), Figure 2: displays average density maps for five 5-HT targets on the common FreeSurfer surface; C) Reproduced with permission from Beliveau et al (2017), Figure 3: displays average density maps for five 5-HT targets on the common MNI152 space (coronal, upper, z = 8mm and sagittal, lower, x = - 3 mm)

1.8 3,4-methylenedioxy-methamphetamine and psilocybin

1.8.1 3,4-methylenedioxy-methamphetamine

3,4-methylenedioxy-methamphetamine (MDMA) is a popular recreational drug which has variously been called an empathogen (Bedi et al., 2010), entactogen (Sumnall, 2006), and the “love drug” (Leneghan, 2013). These names allude to the potent emotional and social effects of the drug, which have been cited as a key reason for its recreational use (Leneghan, 2013; Sumnall, 2006). MDMA elicits the release of dopamine (DA), noradrenaline (NA) and serotonin (5-HT) (de la Torre et al., 2004), with the latter of these believed to be primarily responsible for its prosocial and euphoric effects (Carhart-Harris et al., 2014; Rothman et al., 2001), due to a 10-fold higher affinity for the 5-HT transporter than either DA or NA receptors (Green et al., 2003).

The mechanism of action for neurotransmitter release is reversal of membrane transporter proteins (5-HTT; de la Torre et al., 2004; Green et al., 2003). This increases the availability of 5-HT (and DA and NE) in the synaptic cleft, resulting in an overall increase in serotonergic activity. MDMA is also a direct agonist of 5-HT2A/C receptors (de la Torre et al., 2004; Green et al., 2003). Furthermore, MDMA acts at trace amine-associated receptor 1 (TAAR1), and this is believed to deplete intracellular monoamine vesicular storage, thus increasing their availability for reverse transport (Pei et al., 2016).

Using specific serotonin receptor antagonists, 5-HT activity has been linked to MDMA-induced increased sociality in rodents, with both 5-HT1A and 5-HT2A receptors being implicated in this effect (Hunt et al., 2011; Morley et al., 2005;

Thompson et al., 2007). Studies in humans have investigated the effect of 5-HT receptor antagonists on subjective ratings of prosociality and mood following MDMA administration. These studies have suggested that 5-HT2A receptors are implicated in these effects (Liechti and Vollenweider, 2001; van Wel et al., 2012), but have failed to find evidence of 5-HT1A receptor involvement; although this may be due to the human pharmacodynamics of the antagonist used in these studies (Hasler et al., 2009; van Wel et al., 2012). Both of these studies used the 5-HT1A antagonist pindolol, and they point out that at the dosage used one can expect approximately 40% receptor occupancy. This occupancy may be too low to block the 5-HT1A receptor actions of interest.

Research investigating the potential mechanisms by which MDMA modulates social cognition in humans is in its infancy, with small number of papers published in the last decade (e.g. Dumont et al., 2009; Frye et al., 2014; Hysek et al., 2012; Kirkpatrick et al., 2014; Wardle et al., 2014; Wardle and de Wit, 2014). These have largely looked at facial affect recognition, questionnaire-based measures of prosociality, and the interactions of these outcomes with changes in plasma levels of oxytocin. No MDMA neuroimaging studies have investigated aspects of social cognition beyond affect recognition, although non-social cognition, MDMA imaging studies have recently been published (Carhart-Harris et al., 2014; Carhart-Harris et al., 2014). One of these found reduced mPFC connectivity and supplementary motor area activity at rest, following administration of MDMA (Carhart-Harris et al., 2014). In 0 I review neuroimaging studies of the Ultimatum Game in detail, and will show that these

areas are implicated in responder behaviour. This suggests that MDMA's effects on social cognition may extend to social decision-making.

1.8.2 Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is the active ingredient of a number of psychedelic mushrooms, known for their characteristic hallucinogenic effects. With its metabolite, psilocin, it is a mixed serotonin agonist, with highest affinity for 5-HT1A and 5-HT2A receptors (Passie et al., 2002). Recent studies have shown psilocybin to modulate facial affect recognition (Kometer et al., 2012; Schmidt et al., 2013). A single study has administered psilocybin to investigate other aspects of social cognition (Preller et al., 2016). Preller et al (2016) found decreased feelings of social exclusion on psilocybin compared to placebo, with a corresponding decrease in activity of the dorsal anterior cingulate cortex. Recent evidence also suggests that psilocybin may be efficacious in treating anxiety disorders and depression (Carhart-Harris et al., 2016; Grob et al., 2011).

Characteristics of psilocybin intoxication include vivid perceptual alterations, disruptions of thought, time distortion, euphoria and changes in mood. Kometer and Vollenweider (2016) discuss in detail the evidence that 5-HT2A receptors are primarily responsible for these effects across serotonergic psychedelics. Here, I summarise part of their discussion. A study using transgenic mice attempted to assess the relative contribution of 5-HT1A and 5-HT2A receptors to the effects of LSD (González-Maeso et al., 2007). They found that 5-HT2A receptor knock-out mice did not exhibit classic psychedelic markers in response to LSD. Studies in humans have investigated the effect of the 5-HT2A receptor

antagonist ketanserin, and found that this compound blocks the hallucinogenic effects of psilocybin (Carter et al., 2005; Kometer et al., 2012; Vollenweider et al., 1998). However, a study with human participants found that the partial 5-HT1A agonist buspirone attenuated some of the subjective effects of psilocybin (Pokorny et al., 2016). The authors hypothesise that 5-HT1A receptor activity may modulate the 5-HT2A effect of psilocybin. Together, these provide strong evidence for the key role of the 5-HT2A receptor in the subjective effects of psilocybin, and its potential interactions with the 5-HT1A receptor. It should be noted that while psilocybin has no affinity for dopamine D1 or D2 receptors (Creese et al., 1975; Passie et al., 2002), Vollenweider et al (1999) provided evidence that some of the subjective effects of psilocybin may be due to an indirect effect on dopamine activity, through serotonergic modulation of dopamine release through agonism at these 5-HT receptors.

A body of research has focused on the mechanisms of 5-HT2A receptor activation by psychedelic compounds (González-Maeso et al., 2007, 2003; González-Maeso and Sealfon, 2009; Moreno et al., 2012, 2011). González-Maeso et al (2007) suggest that psychedelic compounds such as psilocybin cause different conformational changes to the 5-HT2A receptor than non-hallucinogenic compounds, thus initiating additional intracellular signalling pathways, a process termed agonist-directed trafficking. Figure 1-4 summarises these findings, which I discuss next.

González-Maeso et al (2007) investigated the transcriptome response to both the hallucinogenic compound (HC) LSD and the non-hallucinogenic compound (NHC) R-lisuride. First they established that both compounds acted at 5-HT2A

receptors. 5-HT receptors are G-coupled protein receptors (GCPR), meaning their intracellular terminal components are associated with so-called G-proteins (Barnes and Sharp, 1999). Ligand binding causes conformational changes of the GCPR which induces G-protein-mediated signalling cascades, with different G-protein subunits being associated with different downstream signalling (Millar and Newton, 2010). 5-HT2A receptor activation has a canonical signalling pathway associated with $G_{q/11}$ proteins, but it has also been shown to be associated with $G_{i/o}$-mediated signalling cascades, via β_{γ} G-protein subunits (Barnes and Sharp, 1999; Kurrasch-Orbaugh et al., 2003). Following the observation that both HCs and NHCs activate $G_{q/11}$-mediated PLC-ß cascades, González-Maeso et al inhibited this pathway. They found that by doing so, both NHC and HC responses were eliminated, suggesting that this pathway was not specific to HC responses.

Building on previous work which had suggested that the $G_{i/o}$-mediated cascade included the tyrosine kinase, src (Banes et al., 1999; Quinn et al., 2002), González-Maeso et al (2007) inhibited this kinase. They found that src inhibition had no effect on the 5-HT2A transcriptome response to NHCs, but had a dramatic effect on that of HCs, as well as HC behavioural markers. Therefore, it is hypothesised that both the $G_{q/11}$ and $G_{i/o}$-mediated signalling cascades are required for psychedelic effect of HCs such as psilocybin. This mechanism has never been examined in humans.

It is unknown whether the psychedelic effects of psilocybin in humans involve the same mechanism, and if so, whether these are also responsible for the

alterations in facial affect recognition. By inhibiting src-kinase in humans it will be possible to investigate the contribution of this pathway to social cognition.

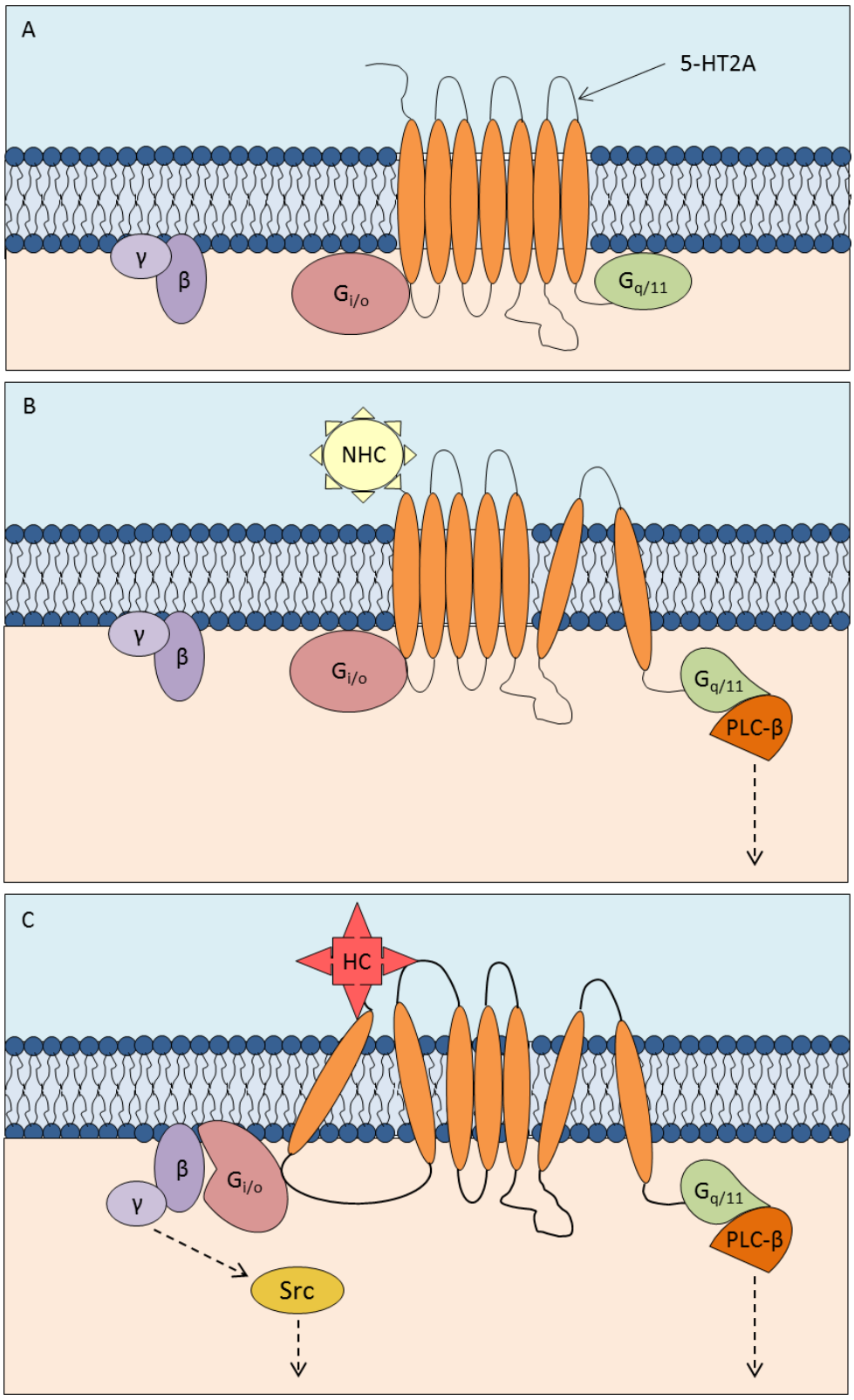


Figure 1-4: Diagram illustrating hypothesised mechanisms underlying hallucinogenic (HC) and non-hallucinogenic (NHC) compound activation of the 5-HT2A receptor. A) Unbound 5-HT2A receptor; B) Shows conformational changes following NHC binding. This allows initiation of phospholipase C-β (PLC- β) cascade; C) Shows hypothesised additional downstream mechanisms of HC binding

1.9 Aims and hypotheses

The aim of this thesis was to investigate the neural and behavioural mechanisms of social cognition, with a focus on social decision-making, empathy and facial affect recognition. To this end I have carried out three main bodies of work, detailed below.

1.9.1 Meta-analysis of Ultimatum Game neuroimaging studies

Chapter 2 will present a meta-analysis of neuroimaging studies investigating the Ultimatum Game (UG). The aim of this chapter is to identify a network of brain regions underlying UG behaviour in healthy adults. As a meta-analysis, this work was hypothesis-free.

The results of this meta-analysis were used to inform the analysis of data collected for the subsequent chapters.

1.9.2 Social cognition following the administration of psilocybin

Chapter 3 will present data collected as part of a study investigating src-kinase inhibition as a potential mechanism for novel antipsychotic development. I present behavioural data of responses to UG offers and an analysis of their relationship to resting-state brain imaging data. This chapter will also present an analysis of facial affect recognition.

Data was collected at three time-points in a placebo-controlled, counter-balanced, crossover design. The first time-point was when participants were being screened for the study and were drug-free. On both other time-points

participants received psilocybin, with prior administration of either a placebo or a src-kinase inhibitor.

The main hypotheses for this chapter are:

1) Psilocybin will decrease rejection rates of unfair offers in the Ultimatum Game, and this decrease will be attenuated by src-kinase inhibition.
2) Psilocybin will impair recognition of negative facial affect.

1.9.3 Social cognition following the administration of MDMA

Chapter 4 will present data from a placebo-controlled, counter-balanced, crossover study investigating the effect of MDMA on social decision-making. In this study participants played the UG and Prisoner's Dilemma during functional neuroimaging. In addition they completed an empathy task and facial affect recognition task outside of the scanner.

The main hypotheses for this chapter are:

1) MDMA will reduce rejection rates of unfair offers in the Ultimatum Game
2) MDMA will increase cooperation in the Prisoner's Dilemma
3) MDMA will enhance emotional, but not cognitive empathy
4) MDMA will reduce recognition of negative facial affect
5) Altered activation of brain regions identified in Chapter 2 will accompany behavioural differences in the UG

Chapter 2 The Ultimatum Game and brain: a meta-analysis of neuroimaging studies

2.1 Overview

This work in this chapter has been published in the journal Neuroscience and Biobehavioural Reviews: Gabay AS, Radua J, Kempton MJ, Mehta MA (2015) The Ultimatum Game and the brain: A meta-analysis of neuroimaging studies. Neurosci. Biobehav Rev 47, 549–558.

Section 1.5.2.1 of this thesis was an edited version of the introduction to this paper, with both additions and omissions. As such the introduction here will contain some material repeated from the Chapter 1.

2.2 Abstract

Social decision-making tasks involve psychological processes key to effective functioning in a complex, social world. The Ultimatum Game (UG) is a widely studied social decision-making task, which models responses to fairness. A number of neuroimaging studies have investigated the UG to identify neural correlates of unfairness and decisions to reject versus accept an offer. We present the first quantitative summary of neuroimaging studies in social decision-making with a meta-analysis of 11 fMRI studies of the UG, including data from 282 participants. Effect-Size Signed Differential Mapping was used to

estimate effect sizes from statistical parametric maps and reported peak information before meta-analysing them. Consistent activations were seen in the anterior insula, anterior cingulate cortex (ACC), supplementary motor area (SMA) and cerebellum in response to unfair offers. Robust activations in the ACC, SMA and putamen were seen when deciding to reject rather than accept UG offers. These are consistent with models of motivational conflict during the UG decision-making process, a response to norm violations, with a possible role for the reward system.

2.3 Introduction

Social interactions often require a balance between emotional and 'rational', cognitive motivations. Examples of this conflict can be seen in everyday life, for example in managing workplace relationships or taking decisions to trust others. The conflict between emotional and cognitive motivation has been studied using social decision-making tasks (Rilling and Sanfey, 2011; Stallen and Sanfey, 2013). Social decision-making tasks are an important model of the interplay between social and emotional cognition and reasoned, self-interest judgments, and are believed to involve psychological processes key to effective functioning in the complex, social world.

The Ultimatum Game (UG) is a task often used to study social decision-making, with its origins in behavioural economics (Güth et al., 1982). In the game one player acts as proposer and another acts as responder. The proposer is given a sum of money and chooses how much to split this with the responder. The

proposer is typically given a range of options as to how to split the sum, but in all cases must offer something. The responder can either accept the division of money, in which case both players receive the amount proposed, or they can reject it, in which case neither player receives any money at all.

According to Rational Choice and Expected Utility Theory, a rational responder in the UG should accept any amount offered by the proposer, as this will represent a gain. Knowing this, a rational proposer should offer the lowest amount allowed by the rules, typically 10% of the total sum (Glimcher et al., 2009). However, evidence shows that people do not behave in this way, with proposers typically offering closer-to-equal amounts, and responders typically rejecting offers they consider to be unfair. Indeed, studies suggest that while people accept fair, or close to fair, offers (40–50%), rejection rates gradually increase as the offer becomes lower (Civai et al., 2012a; C. Corradi-Dell'Acqua et al., 2013; Güth et al., 1982; Oosterbeek et al., 2003; Rilling and Sanfey, 2011). This finding has been found across cultures (Henrich et al., 2005; although see Oosterbeek et al., 2003) and is interpreted as being a result of social influences on decision-making. This interpretation is supported by the consistent finding that when the same offers are made in a non-social control condition, typically where it is clear the offer has been computer-generated, rejection rates fall close to zero (e.g. Sanfey, 2003). Thus it is suggested that responders are punishing violations of social norms despite the cost incurred to them, which has been argued to be an adaptive mechanism (Boyd et al., 2003; Nowak et al., 2000; Rand et al., 2013).

Sanfey et al. (Sanfey, 2003) were the first to investigate the neural basis of motivational conflicts during decision-making in the UG. They argue that the decision to forego a financial gain is a response to the negative emotion elicited by unfair treatment. In order to investigate this, neural activity following receipt of unfair offers was contrasted with activity following fair offers. In this study, offers of 30% or below of the total stake were considered unfair. The authors discussed increased activations seen in the anterior cingulate cortex (ACC), anterior insula, and the dorsolateral prefrontal cortex (DLPFC). They suggest that anterior insula activity was predictive of the decision to reject an unfair offer, and argued that this area not only represented the negative emotion associated with unfairness, but also drove the decision to reject unfair offers.

Follow-up studies have similarly investigated fairness in the UG, with others reporting differences in activation associated with the decision to reject versus accept an offer. In the imaging literature there is some variation in the threshold below which offers are considered unfair, ranging from 20% to 40% of the total stake (see Table 2-1 for the definition of unfair for each of the included studies in the present analysis). This lack of consensus represents a challenge for the field, as an “unfair” offer in one study may not engage the same processes as an “unfair” offer in another study. Indeed, it has been reported that responses to 30% offers are dependent on the context in which they are presented, with lower rejection rates when there are more offers of 10–20% than 40–50%, and vice versa (Wright et al., 2011). An aim of the current analysis was to see if this variation in definition of “unfair” had a modulatory effect on the neuroimaging results.

Neuroimaging studies have investigated variables such as the context of gain or loss (Guo et al., 2013a; Tomasino et al., 2013a), variations across the lifespan (Katia M. Harlé and Sanfey, 2012) and the influence of competition (Halko et al., 2009a) and emotional states (Grecucci et al., 2013; Katia M. Harlé et al., 2012) on UG behaviour.

Across studies, there is an apparent consistency in the areas involved in social decision-making in the UG, and there have been a number of reviews published which summarise neuroimaging studies of social decision-making (Lee and Harris, 2013; James K Rilling et al., 2008; Rilling and Sanfey, 2011; Stallen and Sanfey, 2013). However, it has been documented that neuroimaging studies are typically under-powered (Button et al., 2013), leading to increased risks of both type I and type II errors. As such, meta-analyses of neuroimaging studies have become increasingly important. To date there has been no attempt at a quantitative analysis of neuroimaging findings in this field.

Social cognitive deficits are well recognised in psychiatric disorders, and have specifically been emphasised in schizophrenia as being a domain requiring urgent research to improve treatment options (Green et al., 2004). Social decision-making is an area of social cognition which is increasingly investigated, and by providing evidence for brain regions consistently involved in this domain, meta-analysis represents an important step in the development of psychopharmacological treatments. To date the UG is the most studied social decision-making task with functional imaging, hence our decision to review it here.

Popular methods of fMRI meta-analysis include activation likelihood estimation (ALE) and multi-level kernel density analysis (MKDA). These methods base their meta-analytic results on coordinates which have been reported by individual studies to have passed the statistical threshold for significance set by those studies. Whilst the results of such analyses provide an informative summary of statistically significant fMRI results across a number of studies in a field, these methods do not include subthreshold results and therefore do not necessarily address the problem of low power inherent in fMRI. A further limitation of these techniques is that they do not produce a statistical measure of effect-size or its variance.

In this analysis, we use Effect-Size Signed Differential Mapping (ES-SDM), a neuroimaging meta-analytic method that can combine reported peak information (coordinates and t-values) from some studies, with original statistical parametric maps (SPMs) from others, thus allowing a comprehensive inclusion of information from these studies (J. Radua et al., 2012). The main advantage of an effect-size-based meta-analysis is the ability to produce a more precise estimate of the effect size than is seen in the individual studies included in the meta-analysis alone. Other relevant advantages are the possibility to assess the between-study heterogeneity and the potential publication bias. Here, we not only use these tools but also assess whether findings are replicable using the so-called jack-knife analyses.

Typically, for the UG, contrasts of interest are those comparing neural activity associated with receiving an unfair offer compared to a fair offer, or activity associated with choosing to reject rather than accept an offer, although not all

studies report both of these contrasts. We present findings from the analysis of both of these contrasts, termed the Fairness and Response contrast, respectively. Where appropriate, additional data has been obtained from the authors. There are four possible outcomes in the UG: acceptance or rejection of a fair offer, and acceptance or rejection of an unfair offer. Figure 2-1 illustrates how these possible outcomes are positioned in each of the contrasts reported in this meta-analysis.

There are different interpretations of UG neuroimaging results. These place different emphasis on the role of negative emotions and the idea of violations of social norms. As mentioned above, it has been suggested that UG rejection behaviour is driven by negative emotion elicited by unfair treatment, and that this is associated with anterior insula activation (James K Rilling et al., 2008; Sanfey, 2003). An alternative interpretation is that anterior insula responses are not driven by negative emotion per se, but by detection of violations of social norms, and that the decision to reject the unfair offer is a rejection of this norm violation (Civai et al., 2012a; C. Corradi-Dell'Acqua et al., 2013). Additionally, a role for reward has been proposed. It has been suggested that reward pathways may be involved in the punishment of norm violations, as well as overcoming negative emotions to accept unfair offers (de Quervain, 2004; Tabibnia et al., 2008). These explanations need not be mutually exclusive, and while a meta-analysis will not be able to select between these interpretations, we will discuss our findings in the context of these models. Here, in order to identify areas most robustly associated with unfairness and rejection behaviour,

we present results from a meta-analysis of functional neuroimaging studies investigating the Ultimatum Game.

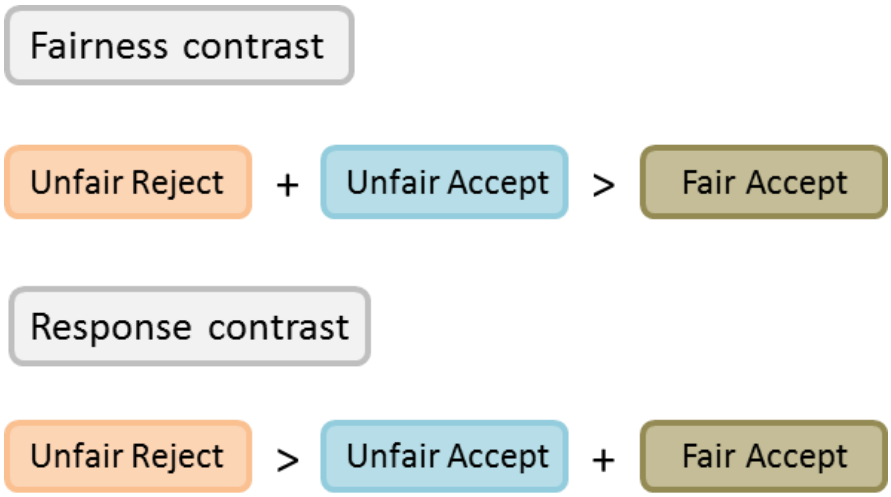


Figure 2-1: Contrast diagram. NB: No 'Fair reject' as the frequency of this outcome was negligible

2.4 Methods

2.4.1 Literature search

A literature search was carried out using the PubMed and Web of Knowledge databases, entering the search terms "Ultimatum Game" AND ("fMRI" OR "functional magnetic resonance imaging") in March 2014. Further papers were identified by searching reference sections in papers returned by the original search. We included studies that (1) reported fMRI results from whole brain thresholds, i.e. excluding those results only obtained after applying small-volume corrections, (2) included healthy participants, (3) used a single-shot rather than iterated version of the Ultimatum Game, (4) reported data from participants acting as Responders rather than Proposers, (5) reported data from

versions of the Ultimatum Game which can be considered equivalent to the standard version of the game (for example, where a study investigated differences between a ‘gain’ or ‘loss’ context, we only included data from the ‘gain’ context). In order to adhere to typical meta-analysis standards, we excluded studies with sample overlap with an already-included study. Eleven studies met these inclusion criteria (see Figure 2-2).

Our primary interest was in the Fairness (Unfair offer vs Fair offer) activation contrasts in participants playing a standard version-equivalent of the Ultimatum Game. Where these contrasts were not reported, authors were contacted asking for the relevant data. Authors were also asked to provide data for the Response contrast (Accept vs Reject) where available, as well as behavioural data in the form of offer rejection rate. Statistical parametric maps (t-maps) were requested from all studies included in the meta-analysis in order to increase the precision and accuracy of the results (for details, see Section 2.4.2).

2.4.2 Effect Size-Signed Differential Mapping (ES-SDM)

The meta-analysis was carried out using Effect Size-Signed Differential Mapping (ES-SDM) software. ES-SDM is a weighted, voxel-based meta-analytic method which has been validated and used in a number of structural and functional MRI meta-analyses (Aoki et al., 2013; Fusar-Poli, 2012; Hart et al., 2012; Nakao et al., 2011; Richlan et al., 2011). ES-SDM recreates voxel-level maps of effect sizes and their variances, and allows the inclusion of both peak information (coordinates and t-values) and statistical parametric maps (J. Radua et al., 2012). The conversion from t-statistics to effect size is carried out using standard statistical techniques. Where statistics are only available for

reported peak coordinates, the effect size is exactly calculated at this peak and estimated in the remaining voxels depending on their distance from these peaks, using an unnormalised Gaussian kernel, which is multiplied by the effect size of the peak. This method of estimation is similar to the estimation of activation likelihood used in ALE, but the use of effect sizes in the calculation has been shown to increase the accuracy of estimation of the true signal compared to alternative methods (Radua et al., 2012). Additionally, the inclusion of statistical parametric maps in a meta-analysis has been shown to substantially increase the sensitivity of voxel-based meta-analyses. For example, in the ES-SDM validation study, sensitivity increased from 55% to 73% with the inclusion of just one SPM and to 87% with the inclusion of two SPMs (Radua et al., 2012). Unlike other methods, ES-SDM allows both negative and positive values in the same map, which, along with the use of effect size and variance maps, allows for standard meta-analytic measures to be calculated, such as between-study heterogeneity. Full details of the ES-SDM method and its validation are presented elsewhere (Radua et al., 2012).

2.4.3 Analyses

Meta-analytic effect-sizes were voxel-wise divided by their standard errors to obtain ES-SDM z-values. As these z-values may not follow a standard normal distribution, a null distribution was empirically estimated for each meta-analytic brain map. Specifically, null distributions were obtained from 50 whole brain permutations (which, multiplied by the number of voxels, resulted in about 4-million values per null distribution); previous simulation work has found that permutation-derived ES-SDM thresholds are already very stable with even only

5 whole-brain permutations (Radua et al., 2012). Voxels with a p-value <0.001 were considered as significant, but those from clusters with less than 10 voxels or with peaks with SDM z-values <1 were discarded in order to reduce the false positive rate. While this threshold is not strictly family-wise correction for multiple comparisons, previous research has found that it has an optimal sensitivity while correctly controlling the false positive rate at <0.05 or even <0.01 (Radua et al., 2012).

In order to assess the potential impact of the variation in definition of unfair offer (See Table 2-1), we carried out a meta-regression analysis on effect size values at peak voxels of significant clusters using the metareg module in Stata Statistical Software (Harbord and Higgins, 2008; StataCorp, 2011). Heterogeneity was also assessed in areas of significant activation. Jack-knife sensitivity analyses were conducted to examine the robustness of the main meta-analytic output. This was carried out by removing one study at a time and repeating the analysis. In order to assess publication bias, effect size estimates were extracted for peak voxels of significant clusters from the meta-analysis for each study. Using these, funnel plots were created and visually inspected, and Egger regression tests carried out (Matthias Egger et al., 1997). We used the Egger regression test as a quantitative method of assessing asymmetry in the funnel plots. Evidence of bias is indicated if the intercept of a regression line of effect size/standard error against 1/standard error significantly deviates from zero.

In addition, we assessed the rejection rate of the responder from each study included in the meta-analysis in order to explore the variation in response

trends across studies. Where behavioural data was supplied by corresponding authors on individual studies, this data was incorporated into this analysis (n = 4). Where this data was unavailable from corresponding authors, graphical behavioural data was digitally measured using the GNU imaging manipulation program (v2.6.1) (Mattis and Kimball, 2008).

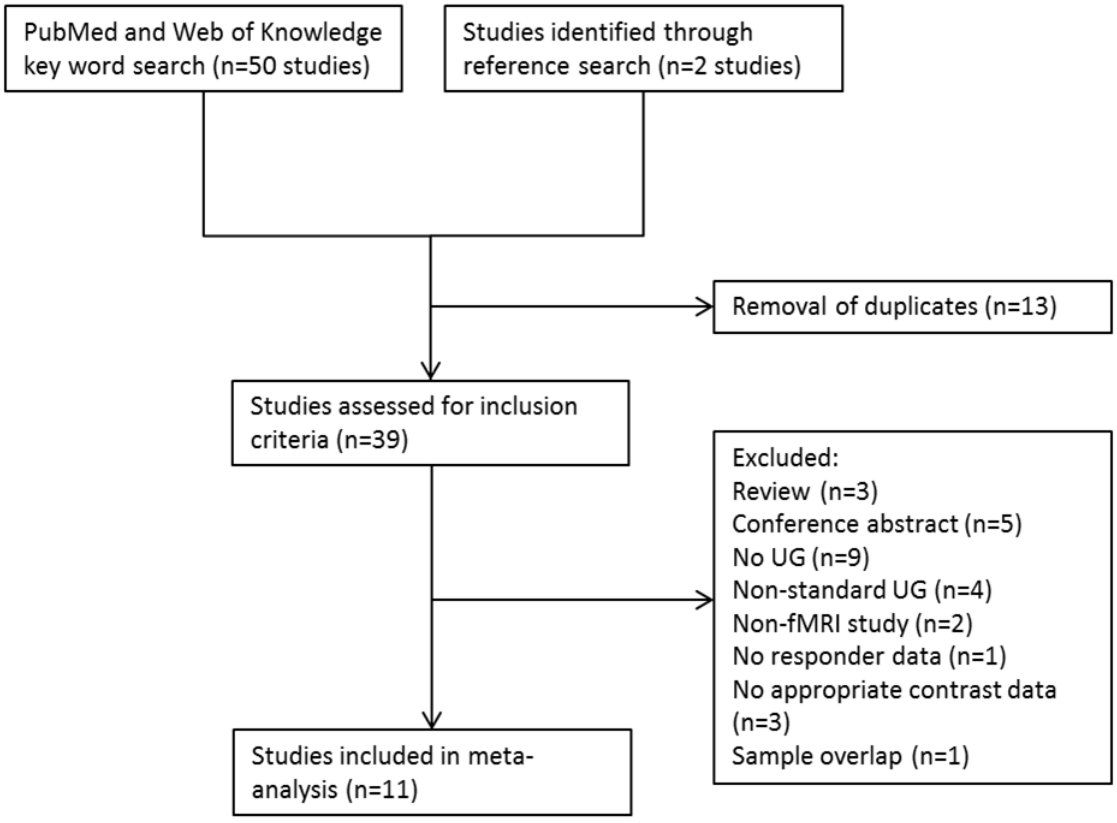


Figure 2-2: Flow chart showing study selection for the meta-analysis

2.5 Results

2.5.1 Included studies

See Table 2-1 for details of included studies. 11 studies were identified for inclusion in the 'Fairness' meta-analysis (Unfair offer > Fair offer)(Baumgartner et al., 2011; Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013; Guo et al., 2013b; Halko et al., 2009b; Katia M Harlé and Sanfey, 2012; Kirk et al., 2011a; Sanfey et al., 2003; Tomasino et al., 2013b; Vieira et al., 2013; Wei et al., 2013). These included a total of 282 participants. The authors of eight studies were able to provide T-maps for use in the meta-analysis (Baumgartner et al., 2011; Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013; Guo et al., 2013b; Halko et al., 2009b; Tomasino et al., 2013b; Vieira et al., 2013; Wei et al., 2013). Five studies were able to provide statistical parametric maps for the 'Response' meta-analysis (Reject > Accept), which included data from 100 participants (Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013; Guo et al., 2013b; Tomasino et al., 2013b; Wei et al., 2013). Six studies were able to provide data for contrasts which were not reported in their publications (Baumgartner et al., 2011; Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013; Guo et al., 2013b; Tomasino et al., 2013b; Wei et al., 2013).

The inclusion of this many statistical parametric maps is a strong asset to the current analysis. The results of the meta-analyses will be less biased toward the reported peaks of studies for which we were unable to obtain T-maps. Additionally, the increased statistical power afforded by the inclusion of a high percentage of T-maps (J Radua et al., 2012) in the analysis enables the

detection of areas of activation which may not have reached statistical significance in any one study alone. As such, the potential exists to highlight new areas for study in the social decision-making field.

Table 2-1: Details of included studies. For studies whose t-maps were not available, the reported results were thresholded as follows: Sanfey et al (2003) – p < 0.001, cluster size >= 10 voxels; Kirk et al (2009) – p < 0.05, FDR-corrected, extend threshold > 10 v voxels; Harlé & Sanfey, 2012 – corrected for cluster-wise significance: p < 0.05, cluster size >= 5

Study	No. of participants	Data	Analysis software	Definition		Behavioural data	Meta-analysis	
				Unfair (mean)	Fair		Fairness	Response
Sanfey et al, 2003	19	Reported peak coordinates	Brain Voyager	10 -30% (18%)	50%	Graphically measured	✓	
Halko et al, 2009	23	T-map	SPM 2	8 - 17% (10.4%)	33 -42%	Actual data	✓	
Kirk et al, 2011	40	Reported peak coordinates	SPM 2	10 -20% (15%)	30 -50%	Graphically measured	✓	
Baumgartner et al, 2011	18	T-map	SPM 5	20 - 30% (15%)	40 - 50%	Actual data	✓	
Harlé & Sanfey, 2012	38	Reported peak	Brain Voyager	10 -30% (20%)	50%	Graphically measured	✓	

		coordinates	v1.1					
Civai et al, 2012	19	T-map	SPM 8	10 -20% (15%)	50%	Actual data	✓	✓
Corradi-Dell'Aqua et al, 2013	23	T-map	SPM 8	10 -20% (15%)	50%	Graphically measured	✓	✓
Guo et al, 2013	21	T-map	SPM 5	10 -40% (21.7%)	50%	Actual data (error bars graphically measured)	✓	✓
Tomasino et al, 2013	17	T-map	SPM 5	10% (10%)	30%	Actual data	✓	✓
Vieira et al, 2013	35	T-map	AFNI	20 – 33%	40 – 50%	N/A	✓	
Wei et al, 2013	29	T-map	SPM 8	10 – 20%	40 – 50%	N/A	✓	✓

2.5.2 Behavioural results

Offers were converted to percentages of the total money available, to enable comparison across studies. Figure 2-3 illustrates the mean rejection rate at each offer level for individual studies included in the meta-analysis.

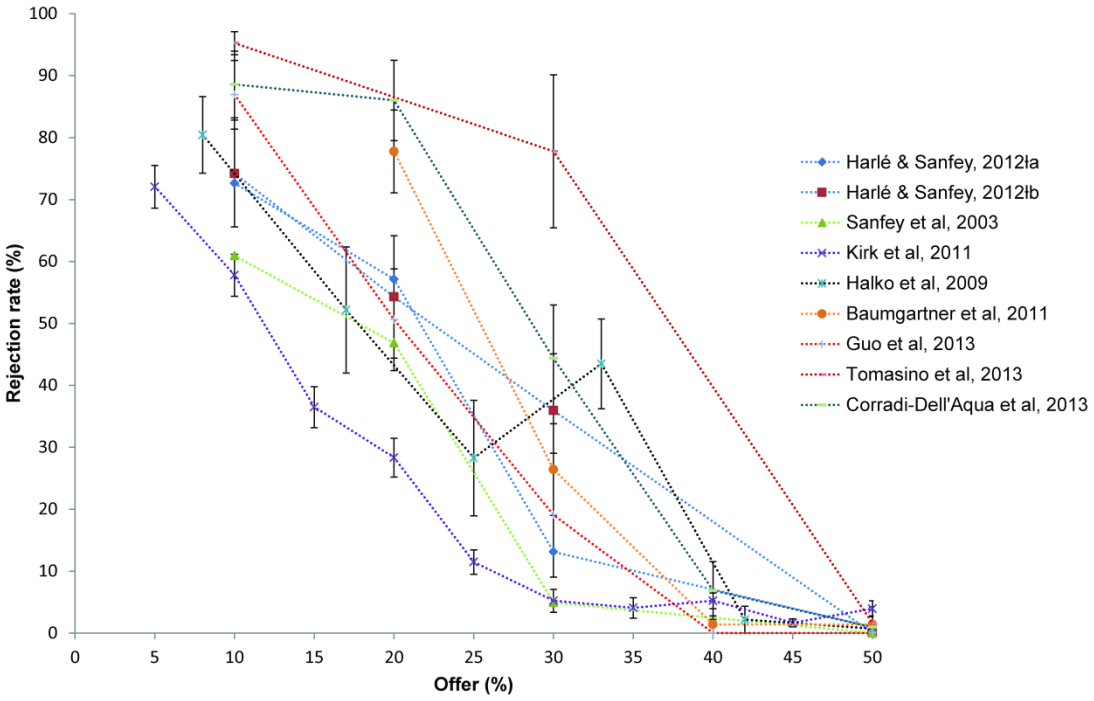


Figure 2-3: Responder rejection rates from behavioural data of the included studies. NB: Civai et al (2012) and Wei et al (2013) not included due to rejection rates not being given for individual offers. Vieira et al (2013) not included because data not available łData from Harlé and Sanfey (2012) reported separately for two participant groups, a Young (18-27) and b Older (55-78). Error bars: ± 1 SEM (standard error of the mean)

2.5.3 Fairness meta-analysis

2.5.3.1 Results of Fairness meta-analysis

This meta-analysis included all 11 studies comprising 282 participants. Participants showed spatially large activations in: a) bilateral mid/anterior cingulate cortex (aMCC/ACC), extending to the left anterior supplementary motor area (SMA); b) bilateral insula; and c) right cerebellum. Additionally, there was a smaller cluster of activation in the left inferior parietal lobule (Table 2-2; Figure 2-4(A)).

2.5.3.2 Fairness contrast heterogeneity, sensitivity and publication bias analyses

Significant between-study heterogeneity was limited to a small area in the cingulate gyrus. Jack-knife sensitivity analyses showed that the main findings were highly replicable across combinations of datasets. However, the activations in the clusters encompassing the left insula appear more robust than those of the right insula. In addition, clusters in the cerebellum and aMCC/ACC appear more robust than the inferior parietal lobule (see Figure 2-5(A)). Three clusters (left precentral gyrus, left postcentral gyrus, right insula) showed evidence of publication bias using Egger. It should be noted that the publication bias analyses would not have survived multiple comparison correction, but we chose to report the conservative figure here.

2.5.4 Response meta-analysis

2.5.4.1 Results of Response meta-analysis

This meta-analysis only included five studies comprising 100 participants, but we could retrieve the statistical parametric maps from all of these studies. Statistical parametric maps highly increase statistical power (J Radua et al., 2012), enabling the detection of a number of robust activation clusters. The results of the response contrast meta-analysis showed increased activation in: a) SMA, extending to the anterior midcingulate cortex (aMCC); b) right middle frontal gyrus; c) bilateral lentiform nucleus. Other, less significant, clusters included the bilateral fusiform gyrus, inferior parietal lobule, and the posterior cingulate (Table 2-3; Figure 2-4(B)).

2.5.4.2 Response contrast heterogeneity, sensitivity and publication bias analyses

There was no significant between-study heterogeneity. Jack-knife sensitivity analyses showed that the main findings were replicable across combinations of datasets, with the most robust findings being in the left aMCC, left SMA and right lentiform nucleus (see Figure 2-5B). There was no evidence of publication bias in all but one cluster, as assessed by the Egger regression test (right superior frontal gyrus) (M Egger et al., 1997).

2.5.5 Comparison of Fairness and Response activations

The meta-analytic output maps were binarised in order to assess the overlap of regions activated both by fairness and response contrasts (see Figure 2-4C). Common activation of areas in the bilateral aMCC and right SMA were found.

2.5.6 Meta-regression to assess the influence of unfair offer definition

In order to assess the influence of the variation of unfair offer definitions across studies on the meta-analytic results, we carried out a meta-regression of the effect size of the peak voxel at each significant cluster. We first calculated the mean unfair offer in each study (range: 10-26.5%, mean: 17.4%), then used these values in the meta-regression. In no cluster across the two contrasts did the mean unfair offer modulate effect size at its peak voxel.

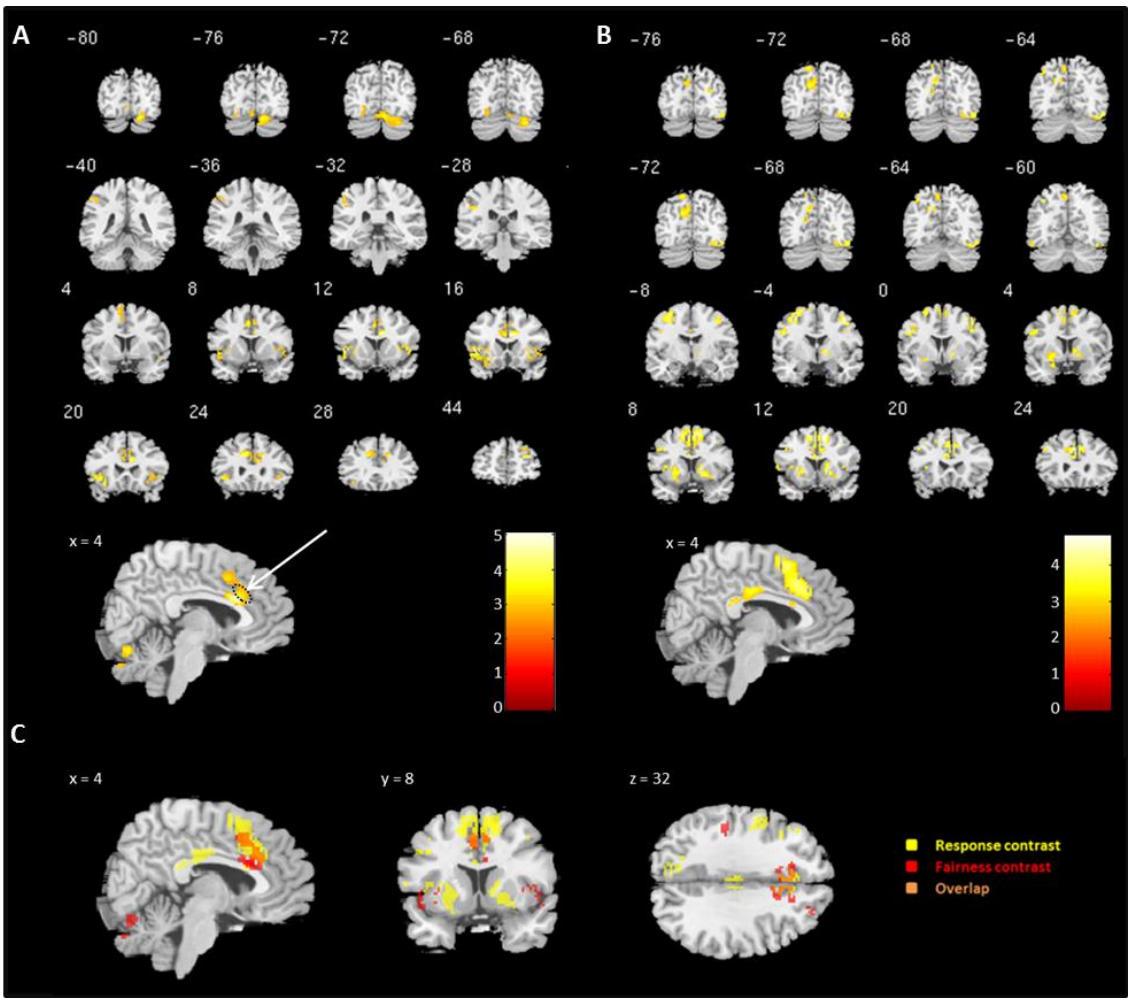


Figure 2-4:A) Fairness contrast results, with small area of between-study heterogeneity labelled on sagittal slice with a dotted outline and arrow B) Response contrast results C) Fairness and Response contrasts binarised; orthogonal views to highlight overlap. Col Colour bars represent z values

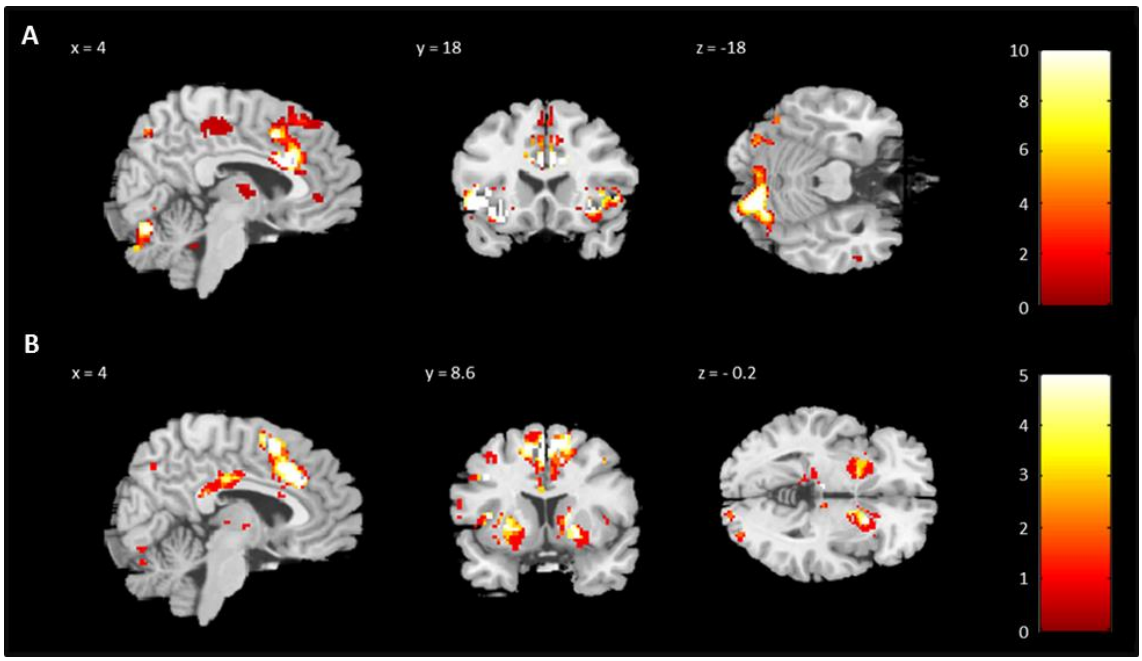


Figure 2-5: Binarised maps of Jack-knife analyses. Colour bars represent number of overlapping jack-knife maps. A) Fairness contrast B) Response contrast

Table 2-2: Meta-analytic results for the Fairness contrast (n = 11, k ≥ 25)

Peak voxel							Cluster	
Region	Talairach			Hedge's g	SDM *z*-value	*p*-value	No. of voxels	Breakdown
	x	*y*	*z*					
Anterior cingulate cortex	6	16	26	0.33	5.142	< 0.000001	678	Bilateral mid/anterior cingulate gyrus Left supplementary motor area
L precentral gyrus	-42	14	6	0.29	4.698	0.000002	349	Left insula Left inferior frontal gyrus Left claustrum
R cerebellum (uvula)	26	-68	-26	0.28	3.731	0.000077	566	Right cerebellum
L postcentral gyrus	-38	-28	30	0.22	3.626	0.000125	123	Left inferior parietal lobule
R insula	40	12	8	0.33	3.606	0.000125	220	Right insula
L lingual gyrus	-26	-70	-8	0.19	3.132	0.000904	88	Left cerebellum

Table 2-3: Meta-analytic results for the Response contrast (n = 5, k ≥ 25)

Region	Peak voxel: Talairach *x*	*y*	*z*	Hedge's g	SDM *z*-value	*p*-value	Cluster: No. of voxels	Breakdown
Left superior frontal gyrus	10	12	52	0.53	4.895	< 0.000001	1285	Bilateral anterior supplementary motor area (SMA) Bilateral anterior midcingulate cortex (aMCC)
Right middle frontal gyrus	38	-4	50	0.47	4.437	0.000001	169	
Right lentiform nucleus	16	10	2	0.43	4.090	0.000045	256	Right caudate body Right lentiform nucleus
Left inferior parietal lobule	-36	-60	46	0.42	3.955	0.000077	101	Left inferior parietal lobule Left superior parietal lobule
Right fusiform gyrus	42	-66	-14	0.41	3.917	0.000093	163	
Left cingulate gyrus	-2	-22	34	0.41	3.875	0.000113	148	Bilateral posterior mid cingulate
Left lentiform nucleus	-20	14	6	0.40	3.832	0.000139	287	
Left precuneus	-18	-68	20	0.40	3.541	0.000434	170	Left precuneus Left cuneus
Left fusiform gyrus	-50	-56	-16	0.36	3.415	0.00061	46	
Right middle occipital gyrus	30	-78	20	0.36	3.398	0.000746	29	Right cuneus
Right insula	38	10	6	0.35	3.340	0.000928	33	
Left precuneus	-12	-70	50	0.34	3.238	0.001308	92	

2.6 Discussion

We present the first meta-analysis of neuroimaging studies of the Ultimatum Game (UG). The UG is a widely used social decision-making task, which models behaviour in response to fairness considerations. By examining the neural correlates of responders in the UG, we aim to build upon the growing body of literature which looks to elucidate the mechanisms by which humans incorporate social and self-interested considerations on a neural level. The results of this meta-analysis indicate that there is a consistent activation of the bilateral mid-anterior insula, aMCC/anterior cingulate cortex (ACC), medial supplementary motor area (SMA), and cerebellum in response to unfairness in the Ultimatum Game (UG). When making the decision to reject rather than accept an offer, activations were seen bilaterally in the aMCC and SMA, bilateral lentiform nucleus, and the right middle frontal gyrus. The results from the Response contrast were most robust in the left aMCC and left SMA. Based on the results of these analyses, there appears to be common activations in response to unfairness and during the decision to reject rather than accept an offer. This overlap occurs in the aMCC and the SMA.

The purpose of the analysis was not to select between the different models used to explain UG behaviour and its neural correlates, but to provide a robust, quantitative definition of the brain regions consistently activated in the relevant contrasts. In so doing, we have discussed the role of each region in relation to the model of norm violations, reward, or affective processing, as appropriate.

Studies have previously found the anterior insula to be involved in processing negative emotional states, such as anger and disgust (Damasio et al., 2000; Phillips et al., 1997). The activation of this region in response to unfair offers in the UG is often interpreted as processing and representing the negative emotional state induced by unfair treatment by a social entity (Halko et al., 2009b; Sanfey et al., 2003). The consistent finding that anterior insula activation is not seen in low, control-condition offers (non-social) is evidence that this is not simply a negative emotional response to low monetary reward (Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013; Katia M Harlé et al., 2012; Sanfey et al., 2003). Some studies report that the strength of anterior insula activation in response to unfair offers is predictive of the decision to reject such an offer (Kirk et al., 2011a; Sanfey et al., 2003). Indeed, Sanfey et al (2003) examined this on a trial by trial basis and concluded that this supported "…the hypothesis that neural representations of emotional states guide human decision-making" (p.1757).

A different interpretation of anterior insula activation is that it is involved in representing a deviation from expected norms, in this case, the violation of social norms (Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013). Civai et al (2012) and Corradi-Dell'Acqua et al (2012) report that anterior insula is activated in response to unequal offers regardless of whether responders are making decisions on behalf of themselves or a third party. Citing investigations of galvanic skin response during a similar study (Civai et al., 2010b), these authors have suggested that responding to third-party offers diminishes the emotional response elicited by unfair offers, despite no observed reduction in

rejection rate. Supporting the interpretation that anterior insula activity represents deviation from expected norms, the study by Civai et al (2012) reported that when participants responded to unequal offers in both directions – i.e. both advantageous and disadvantageous – for themselves or a third party, they rejected inequality on behalf of a third party regardless of advantageousness, while only rejecting disadvantageous inequality in the self-trials. Interestingly, not only was the anterior insula activated in response to both self and third-party inequality, but increased activation was *not* observed in disadvantageous unequal compared to advantageous unequal offers to the self. Furthermore no correlation was found between strength of anterior insula activation and rejection rate. This suggests that the role of the insula upon receipt of an unfair offer goes beyond representing negative emotions.

The activations seen in the medial prefrontal and cingulate cortices have been interpreted as representing the control and monitoring of conflict between emotional and cognitive motivations (Baumgartner et al., 2011; Sanfey et al., 2003). The fact that there is overlap in these areas in both the Fairness and Response analyses presented here appears to support this interpretation. Referring to Figure 2-1, it is clear that the Fairness contrast encompasses the decision to both accept and reject unfair offers; the Response contrast represents the cognitive, motivational conflict involved in rejecting an unfair offer. As such both contrasts would be expected to identify a conflict between emotional and cognitive motivations. It should be noted that while these results appear to be in line with the conflict monitoring/resolution model of ACC/mPFC function, there is debate as to the validity of this model (Fellows and Farah,

2005; Grinband et al., 2011; Holroyd, 2013). Grinband and colleagues (2011) suggest that mPFC activation (including mid-anterior cingulate) in conflict resolution paradigms is better explained in relation to reaction/response time, with greater activation seen with longer response times. Few studies report reaction times in the UG, so a meta-regression was not possible, and there is inconsistency between those that do (Katia M Harlé and Sanfey, 2012; Tomasino et al., 2013b; Van der Veen and Sahibdin, 2011). While the findings of the current analysis confirm the role of this area in social decision-making and the UG, we are unable to resolve the debate with this data.

Reports that the aMCC/mPFC are activated more in response to unfair offers to the self than to third parties, and that this activation is negatively correlated with rejection rate, supports the argument that these areas are involved in overcoming the motivation to sanction norm violations in favour of self-interest following receipt of an unfair offer (Civai et al., 2012b; Corrado Corradi-Dell'Acqua et al., 2013). In a recent review, Apps et al (M. a J. Apps et al., 2013) argue that the midcingulate cortical gyrus is intimately involved in the processing of social information, specifically when predicting and monitoring the outcomes of decisions during social interactions. The results from the Fairness and Response contrasts support this. Nachev et al (2005) argue that the rostral and caudal regions of the pre-SMA, seen in the present analyses, are functionally distinct in free-choice action planning, with the overall role being to resolve competition between two incompatible action plans. The authors suggest that alterations in planned action will be represented in the pre-SMA, and this interpretation can be applied to decision to reject unfair offers (rather

than act in economic self-interest), which is on the same side of both the Fairness and Response contrast.

Interestingly, activation in the dorsolateral prefrontal cortex (DLPFC) was not present in the Fairness contrast, despite this being reported in a number of studies (Baumgartner et al., 2011; Guo et al., 2013b; Güroğlu et al., 2011a; Katia M Harlé and Sanfey, 2012; Sanfey et al., 2003). Meta-analysis seeks to identify consistency in activation across studies. As the DLPFC encompasses a large area, the fact that it is minimally present in this contrast may reflect the disparate regions within this area being activated in different studies. Right DLPFC activation was, however, present in the Response contrast, although sensitivity analyses show the robustness of this finding was less than cingulate and medial prefrontal regions. Studies employing repetitive transcranial magnetic stimulation (rTMS) have shown that disruption to the right DLPFC results in reduced rejection rates of unfair offers (Baumgartner et al., 2011; Knoch et al., 2006, 2008). Baumgartner et al further reported reduced connectivity to the posterior ventromedial PFC (vmPFC), but no differences in activity of, nor connectivity with, the anterior insula. rTMS did not affect participants' fairness ratings of different offers (Knoch et al., 2006, 2008). With anterior insula response to inequality still intact with disrupted right DLPFC, it suggests that DLPFC connectivity to the vmPFC may be key in *implementing* the costly, normative decision to reject unfair offers. It should be noted, however, that vmPFC activity was not seen in the current analysis, and we were unable to look at connectivity as it was not reported in the included studies. A limitation of ES-SDM, other neuroimaging meta-analytic methods and reporting

of imaging results is that there are no standards in place for the meta-analysis of functional connectivity data.

Despite the finding of increased activation in the anterior putamen in the Response contrast analysis, little attempt has been made in the included studies to interpret this, although the reward system has been discussed in relation to its activation upon receipt of a fair offer (Tabibnia et al., 2008). Kirk et al (2011) cite a study which reported putamen activation in a non-social, decision-making investment game when it was revealed that an alternative decision by the participant could have earned an alternative reward to that which they actually earned (Lohrenz et al., 2007). This is termed the "fictive error", which could plausibly explain the activations seen following offers which were later rejected – as these were mostly unfair offers. This interpretation does not elucidate the degree to which this activation is due to social processing. An interpretation which involves social processing draws on the idea of altruistic punishment, the costly punishment of social norm violation. It has been suggested that while the experience of disadvantageous inequality is in itself negative, the opportunity to resolve this inequality is rewarding (de Quervain et al., 2004; Yu et al., 2013), leading to activation of the putamen and related striatal structures. A recent review (Jamil P Bhanji and Delgado, 2014) discusses the evidence for non-social reward pathways being involved in social reward. The evidence suggests there is no distinct social reward pathway, but social rewards, such as sanctioning norm violators, can activate reward areas despite monetary loss (Crockett et al., 2013; de Quervain et al., 2004). Considering the positioning of the possible responses (see Figure 2-1), it is

clear that putamen activation is only seen when acceptance of an unfair offer is not on the same side of the contrast as rejection of an unfair offer. This provides some support for the idea of rejecting an unfair offer being inherently rewarding.

This meta-analysis has highlighted the involvement of another region not discussed in the UG literature: the cerebellum. A recent meta-analysis of cerebellar function highlights a region, close to those activated in our analysis, as being involved in negative emotion (Keren-Happuch et al., 2014). Activity of this area in the Fairness contrast fits with the theory that the cerebellum has a general cognitive-affective role (Keren-Happuch et al., 2014; Schmahmann and Caplan, 2006), but it is unclear from this analysis whether it plays a specific part in the social decision-making aspect of the UG. Referring again to Figure 2-1, the difference between contrasts is the positioning of the decision to accept an unfair offer. The finding of cerebellar activity when both responses to unfair offers are on the same side of the contrast (Fairness) supports an affective processing role for the cerebellum; be this due to negative emotion elicited by unfair treatment, or to inequality aversion. There is large cerebellar-cortical connectivity, and investigation beyond the scope of this meta-analysis is needed to elucidate the role of the cerebellum in social decision-making.

One strength of the current study is that we were able to obtain statistical parametric maps for 8 of the 11 studies included in the analysis. However, there remains the possibility of bias toward the areas of peak coordinates reported in the remaining 3 studies. Running the analysis with just those studies for which we had t-maps produced results similar (though expectably slightly less significant) to those reported here, so any bias introduced appears to be

minimal. The Response contrast consisted of only five studies, so the results from this contrast should be treated with some caution. However, it must be noted that we could retrieve the statistical parametric maps from all of these studies, thus highly increasing the statistical power (J Radua et al., 2012). As with all meta-analyses, inclusion criteria needed to be strict to limit heterogeneity, and as such many fMRI studies in the UG field were necessarily not included in the analyses. This may add an additional unintentional level of bias to the findings reported here.

It is notable that very few neuroimaging meta-analyses address the issue of publication bias. Publication bias analysis in neuroimaging is an area which requires further consideration in the field as a whole, as interpretation of its results are not as straightforward as in traditional meta-analyses. Firstly, there is a relatively low plausibility of a whole-brain analysis not being published due to a low effect in a particular voxel. Secondly, voxels whose effect failed to survive multiple comparisons in an individual study will have an estimated effect size of zero in a coordinate-based, voxel-wise meta-analysis (i.e. in the absence of a statistical parametric map). Studies with small sample sizes will more likely have small effects not reaching significance. Ultimately, this will affect the standard analysis of a funnel plot. However, we have reported the results of the publication bias analysis here to stay in line with standard meta-analysis methods and because the majority of our data included whole brain statistical parametric maps. Furthermore, we do not believe publication bias is any less of an issue as it is in other fields. With these limitations in mind, Egger regression analyses revealed asymmetry in the funnel plots of the peak voxel of 3 clusters

in the Fairness contrast, and 1 in the Response contrast. Visual inspection of these funnel plots suggest that some relatively smaller studies reporting small effects at these voxels are not included in the analysis.

2.7 Conclusion

This study presents the first meta-analysis of functional neuroimaging studies investigating social decision-making. Specifically, Fairness and Response contrasts in the Ultimatum Game. Consistent activations were seen in the anterior insula, aMCC, ACC, and mPFC in response to unfair compared to fair offers. These activations are consistent with a model of norm violations. This analysis has also identified a potential role for the cerebellum in social decision-making. Robust findings of activation in the aMCC, mPFC and putamen were seen during the decision to reject as compared to accept UG offers. This is most parsimoniously explained by conflict during the decision-making process, with a possible role for the reward system, which may have a social element to it.

2.8 Acknowledgement

We are very grateful to those authors of included studies who provided statistical parametric maps and behavioural data for inclusion in this analysis, in some cases carrying out additional analysis on their raw data.

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Chapter 3 The effect of psilocybin on social cognition

3.1 Overview

This chapter examines the influence of the mixed serotonin receptor agonist psilocybin on social decision-making and emotion recognition, as measured by the Ultimatum Game (Güth et al., 1982) and the Affective Bias task (Bland et al., 2016) respectively.

Section 3.2 will introduce the study reported in the chapter. Section 3.3 will outline the version of the Ultimatum Game used in this study, and assess its validity in terms of replicating the findings in the literature and its test-retest reliability. Section 3.4 will then present the method, results and discussion of the study examining the effect of psilocybin on social cognition.

3.2 Introduction

As outlined in Chapter 1 (Sections 1.3 and 1.5.3), there is growing interest in how social cognition, including emotion recognition and social decision-making, is altered in psychiatric conditions (e.g. Bora and Pantelis, 2016; Csukly et al., 2011; Dalili et al., 2015; Destoop et al., 2012; McClure et al., 2007; Polgár et al., 2014). 0 (Section 1.4) provided evidence that current treatments do not do enough to address the emotion recognition deficits seen in schizophrenia (Gabay et al., 2015). In order to understand the mechanisms underlying different aspects of social cognition, studies in healthy volunteers are extremely

important, as samples can be more homogenous than studies with patients exhibiting variations in impairments. Furthermore, when studying the effect of pharmacological interventions, one can study the drug response in the absence of pathological mechanisms, which in turn is important for developing an understanding of the processes affected by the intervention.

Although the psychopharmacology is poorly understood, there is some evidence from studies with healthy individuals that social cognition, including emotion recognition and social decision-making, is modulated by the serotoninergic system (e.g. Crockett, 2009; Hysek et al., 2012, 2013; Schmid et al., 2014; Stewart et al., 2014). Selective serotonin reuptake inhibitors (SSRIs), which increase the synaptic availability of serotonin, have been shown to alter emotion recognition in healthy volunteers, such that there was an increase in recognition of fearful and happy expressions (Browning et al., 2007; Harmer et al., 2003a). Acute SSRI administration has also been associated with reduced accuracy in recognition of angry and sad expressions (Capitão et al., 2015). Contrary to both of these findings, Alves-Neto et al. (2010) showed *improved* accuracy in recognition of sad expressions and *inhibited* recognition of happy expression following single-dose administration of the SSRI escitalopram; a relatively small sample size of twelve participants should be noted for this study, however.

Limiting serotonin availability through tryptophan depletion has produced conflicting results, with Harmer et al. having shown a reduction of fear recognition (Harmer et al., 2003b), while others found no behavioural differences (Fusar-Poli et al., 2007; Grady et al., 2013). Furthermore, the potent

serotoninergic compound 3,4-methylenedioxy-methamphetamine (MDMA), which increases serotonin availability as well as being a direct serotonin 2A receptor agonist, has been shown to reduce the recognition of sad, angry and fearful facial expressions (Bedi et al., 2010; Matthew G Kirkpatrick et al., 2014; Schmid et al., 2014).

The studies detailed above show some variation in their findings. Reasons for this may include the difference in pharmacological agents used; for example, differences in SSRI (citalopram vs fluoxetine vs escitalopram). Additionally, there are a number of serotonin receptors, with a range of downstream mechanisms (Barnes and Sharp, 1999; Hoyer et al., 2002). Treatment with SSRIs and tryptophan depletion do not have a nuanced effect on the serotonin system – they increase or decrease global 5-HT availability, rather than alter activity of specific receptor subtypes – possibly adding to the heterogeneity of the results obtained in the discussed studies of emotion recognition.

The psychopharmacology of social decision-making is discussed in detail in 0 (Section 1.6). Here I will briefly recap the main points relating to the serotonin system and the Ultimatum Game.

As detailed in Chapter 1 (Section 1.5), the Ultimatum Game (UG) was developed in the field of behavioural economics (Güth et al., 1982), and is often used to investigate responses to violations of social norms. In the game one player acts as proposer and another acts as responder. The proposer is given a sum of money and chooses how much to share with the responder. The responder can either accept the division of money, in which case both players receive the amount proposed, or they can reject it, in which case neither player

receives any money at all. Whilst there is a range of strategies of how people respond to monetary offers in this context, most people typically reject low offers (e.g. Gabay et al., 2014; Güth et al., 1982; Sanfey, 2003).

Tryptophan depletion has been shown to increase rejection rates of low offers, while treatment with SSRIs have been shown to *reduce* the rejection of low offers in the UG (Crockett et al., 2008; M. J. Crockett et al., 2010, 2013). Furthermore, it has been reported in a study investigating the UG that participants who rejected low, unfair offers had lower platelet serotonin levels than those who accepted these offers (Emanuele et al., 2008). In a naturalistic study, Stewart et al. (2014) reported increased generosity while playing the UG after taking MDMA; this was quantified as the difference between the highest amount offered and the lowest amount accepted.

As mentioned above, there are a range of serotonin receptor subtypes (Barnes and Sharp, 1999; Hoyer et al., 2002). Having established that the serotonin system is implicated in social cognition, it would be beneficial to establish if specific receptor subtypes underlie this serotonergic effect. As such, the current study investigated the influence of the psychedelic compound psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine). Psilocybin's primary metabolite, psilocin, is a mixed serotonin agonist, with highest affinity for 5-HT1A and 5-HT2A receptors (Passie et al., 2002). Schmid et al (2013) found no effect of psilocybin on the ability to discriminate happy from neutral faces, but reported an impairment in the ability to discriminate fearful faces from neutral faces. Kometer et al (2012), on the other hand, have shown that psilocybin improves recognition of positive, but not negative, facial affect; an effect that was

reversed by pre-treatment with the 5-HT2A receptor antagonist ketanserin. Furthermore, psilocybin has been shown to alter processing of social interactions such that Preller et al (2016) reported a reduction in feelings of experimentally-induced social exclusion with psilocybin compared to placebo.

The pharmacology of psilocybin was discussed in detail in 0 (Section 1.8.2). Here, I will briefly reiterate the pertinent points for this study. Evidence suggests that the psychedelic effects of psilocybin – which include vivid perceptual alterations, disruptions of thought, time distortion, and euphoria – are largely driven by direct agonist action at the 5-HT2A receptor (Nichols, 2004; Vollenweider and Kometer, 2010). This is supported by a body of research in both rodents and humans (e.g. Carter et al., 2005; González-Maeso et al., 2007; Vollenweider et al., 1998). Figure 3-1 (reproduced from Section 1.8.2) shows how conformational changes of the 5-HT2A receptor following binding by classic psychedelics (of which psilocybin is an example) initiates a specific intracellular signalling pathway, mediated by src kinase. Blocking this pathway in rodents has been shown to eliminate psychedelic behavioural markers (González-Maeso et al., 2007).

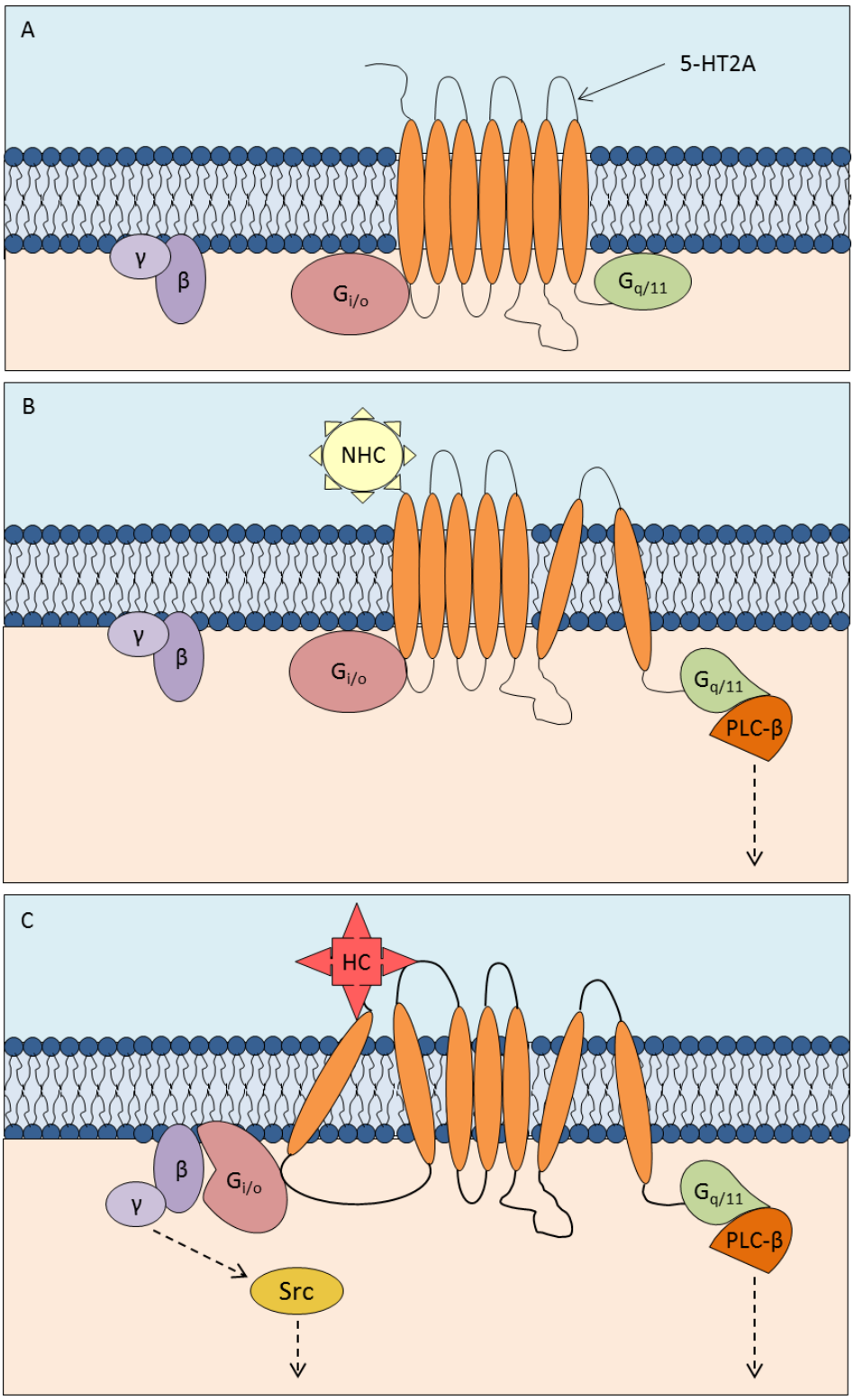


Figure 3-1: Diagram illustrating hypothesised mechanisms underlying hallucinogenic (HC) and non-hallucinogenic (NHC) compound activation of the 5-HT2A receptor. A) Unbound 5-HT2A receptor; B) Shows conformational changes following NHC binding. This allows initiation of phospholipase C-β cascade; C) Shows hypothesised additional downstream mechanisms of HC binding

Saracatinib is a src-family kinase inhibitor developed for solid tumour therapy (Hennequin et al., 2006). It is an investigational compound which, due to its specific inhibition of src and fyn kinases, has been repurposed and tested in a phase Ib clinical trial testing for safety, tolerability and nervous system availability in Alzheimer's disease (Nygaard et al., 2015). This study showed acceptable tolerability and safety at a range of doses, as well as dose-dependent levels of the compound in cerebral spinal fluid, suggesting crossing of the blood-brain barrier. By using this compound in the present study, we aimed to investigate if we can attenuate any psilocybin-induced changes in social cognition in healthy volunteers. Attenuation of these effects by src kinase inhibition would provide strong evidence of 5-HT2A involvement in these processes.

In this study, we first aimed to investigate the effect of psilocybin and saracatinib on social decision-making by looking at responses to a range of offer levels in the UG. This task was completed outside of the scanner. Task-free resting state fMRI data was collected while participants were infused with the psilocybin. As such, I was able to carry out an exploratory analysis investigating the functional connectivity of regions identified in the meta-analysis reported in 0 (Gabay et al., 2014). The aim of this analysis was to investigate whether any changes in UG behaviour across experimental sessions could be associated with changes in connectivity of the UG seed regions as a result of the pharmacological manipulations. Due to the time delay during the collection of this data and completion of the UG, this data must be treated with appropriate caution.

We also had participants carry out a facial affect recognition task outside of the scanner. In addition, we aimed to investigate the effect of pre-treatment with the src-family kinase inhibitor, saracatinib, on these measures. We hypothesised that psilocybin would reduce rejection rates of unfair offers in the UG. We also hypothesised an effect of psilocybin on affect recognition, such that an improved accuracy for positive emotions and reduced accuracy of negative emotions would be found. Additionally, we hypothesised that pre-treatment with saracatinib would attenuate these effects.

In the following section I will introduce the version of the Ultimatum Game used, and present a study designed to test its validity.

3.3 Validation of the Ultimatum Game task design

3.3.1 Abstract

The Ultimatum Game (UG) is a task increasingly used in cognitive neuroscience to investigate prosociality, self-interest, and responses to (un)fairness. Modulation of performance in this task in pharmacological studies would provide insights into its neural underpinnings. Such approaches require that performance stability is known so that appropriate designs of adequate power can be planned. We have carried out a test-retest reliability study to aid design and interpretation of future modulatory studies of the UG. 15 (6F) participants completed the UG at least one week apart. To assess reliability across sessions, variance components were extracted from a generalized linear mixed effects model, with each participant entered as a random effect. This enabled comparison of within- and between-participant variance. Performance in the task itself was also assessed, using the generalized estimating equations method. The task showed good test-retest reliability (Rs ranging from 0.68 – 0.82). Participants rejected a low offers (10-20%) more when they believed the offer came from a real person compared to when it was explicitly received from a computer ($\chi^2_{(1,16)} = 14.69$, OR = 0.31, $p < 0.001$). As such, this task is not only reliable for use in multi-session studies, but also produces results in line with the established UG literature.

3.3.2 Introduction

The Ultimatum Game (UG) is a task developed in the field of behavioural economics which has been introduced in detail in 0 (Sections 1.5) of this thesis.

Most neuroimaging studies investigate UG responses, rather than proposals (Civai et al., 2012a; Civai, 2013a; C. Corradi-Dell'Acqua et al., 2013; Sanfey, 2003), and this is the approach taken in the current version of the task. Researchers frequently present UG offers to participants on a computer, rather than have live partners play the game with them. In order to ensure study participants believe the offers are genuine, different cover-stories are created about where the offers originate. In the current version of the game, participants were told that the offers were collected as part of another study in the wider research project. Participants were led to believe that previous participants would be paid a proportion of the money earned, based on the responses of the participants in the current study. They were also told that their own financial reimbursement was linked to their responses in the game.

When conducting a repeated-measures psychopharmacological study it is important to have an understanding of the test-retest reliability of the tasks being used to assess the behavioural effect of an intervention. That is, whether in the absence of any pharmacological intervention, will people behave similarly across multiple sessions? If a test has poor test-retest reliability, the large variance of the within-participant responses could make it difficult for an effect of the pharmacological intervention to be detected, particularly if the effect size is small. It may also be the case that the process being measured is not stable

(e.g. continued learning). This has implications regarding the sample size required to detect an effect and the amount of training required for participants.

The current study was designed to assess the test-retest reliability of the version of the UG used in the psilocybin study. In addition, we report the outcome of the first session to compare the results to those in the literature.

3.3.2 Methods

3.3.2.1 Participants

Seventeen participants were recruited by advertising through King's College London's research volunteer portal. Of these, two participants did not complete both sessions, so all data analyses are based on 15 datasets (6 F; mean age 21.3yrs, range 19-27yrs). While the drug study reported in this chapter (Section 3.4 below) only included male participants, both genders were included in this validation to make the results more generalizable. Participants played a repeated, single-shot UG on two separate occasions at least one week apart (mean: 7.7 days; range: 7 – 10 days). Written informed consent was obtained from each participant, and ethical approval granted by the King's College London's Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM 14/15-10).

3.3.2.2 Procedure

This version of the UG has three 'offer origin' conditions: first-party (FP), third-party (TP) and random computer-generated offer (GS). Only the FP and GS

conditions will be reported here, as these are the only conditions used in the psilocybin study.

In the FP condition, participants made a decision to reject or accept an offer made directly to them. The premise of this condition is that both they and the proposer will be affected by their response. In the GS condition, the participant is told that the offer they receive is a random, computer-generated offer. In this condition, their decision solely affects their own payoff. Participants were told that they would be paid one percent of the total amount they earn during the course of the study; in reality participants were paid a fixed sum of £20.

While the majority of published studies investigate offers from 10-50% of the total stake, the present study includes “hyper-fair” offers of 80 and 90%. All offers were out of a total stake of £20, so an 80% offer equates to £16. The number of each offer level is given in Table 3-1. The same offers were presented in each offer origin condition; thus participants received a total of 144 offers, split across two runs of the task. Figure 3-2 shows the order of presentation and timing of each round of the task. See Appendix B for the task instructions.

Table 3-1: Number of each offer level and the fairness level assigned for the sake of analysis

Offer level (%)	Number of offers at this level	Fairness level
10	8	Unfair
20	8	
30	4	N/A
40	4	
50	8	Fair
80	8	Hyper-fair
90	8	

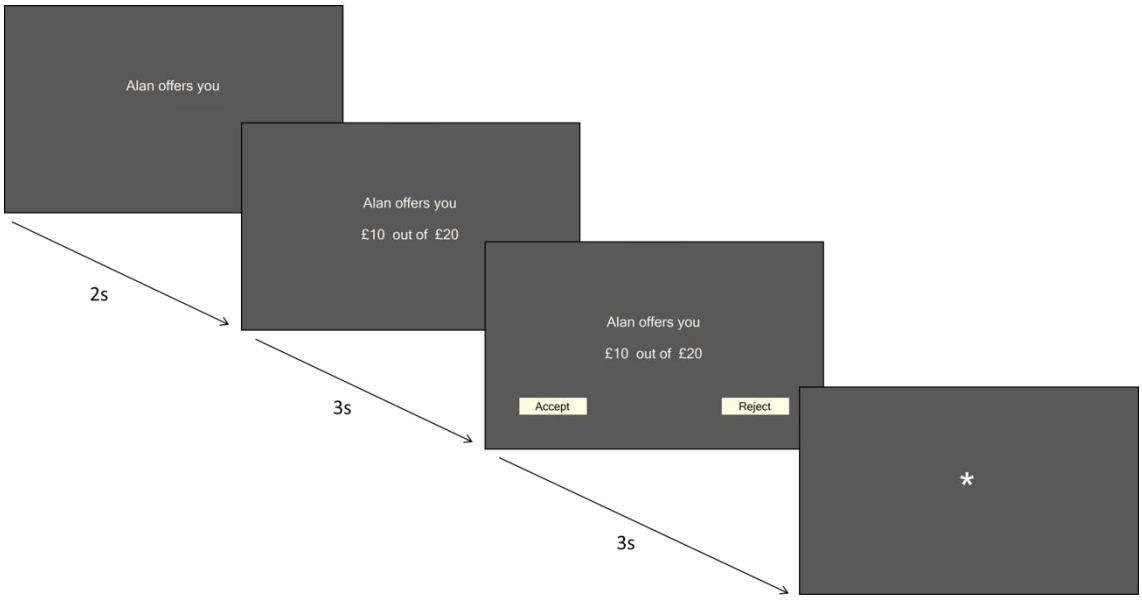


Figure 3-2: A single round from the UG version tested here. First participants are told who is making the offer, they are then told what the offer is, before being asked to either accept or reject that offer

3.3.2.3 Data analysis

The raw data comes in the form of dichotomous accept/reject decisions for each offer. There were 16 offers each from the unfair and hyper-fair levels, and eight fair offers. Participants completed the task during two separate sessions, and the test-retest reliability was tested across these two sessions.

Test-retest reliability

A popular statistic for test-retest reliability is the intraclass correlation coefficient (ICC) (Shrout and Fleiss, 1979). The ICC gives the proportion of the total variance (between- and within-participant) that can be explained by the between-participant variance, with a maximum value of one indicating no within-

subjects' variability. As the method uses the variance components of a repeated-measures ANOVA, it is not an appropriate measure for non-Gaussian data such as the binomial or proportion data collected here (Nakagawa and Schielzeth, 2010).

I have used the rptR package (version 0.6.405, Nakagawa and Schielzeth, 2010) implemented in the R statistical environment (R Development Core Team, 2015). I entered each participant as a random effect into a generalised linear mixed model (GLMM) and extracted variance components to obtain an estimate of repeatability on a logit-link scale. An estimate of more than 0.6 was considered an acceptable level of reliability. This represents 60% of the total variance being explained by between-participant variance.

Outcome of session one

In order to assess whether participants completing this version of the UG behave similarly to the behaviour reported in the UG literature, I took the first session as an example and analysed the data from this session. The data collected was in the form of categorical (accept or reject) responses to monetary offers. Converting this data to proportions and analysing with an ANOVA is problematic on two fronts. First, the proportion data is non-normally distributed. Second, variance of binomial distributions do not show homogeneity, thus violating the assumptions of ANOVA (Jaeger, 2008).

As such, the current data have been analysed using repeated-measures logistic regression, implemented with generalized estimating equations using IBM SPSS Statistics for Windows (IBM Corp., 2012). This is a nonparametric test

which takes into account the correlation of responses within subjects, and produces a chi-squared statistic (χ^2), an odds ratio (OR) and its 95% confidence interval (CI), and a *p*-value. It is a recommended approach to analysing categorical data that has been used in a number of studies in the UG literature (M. J. Crockett et al., 2013; Hanley et al., 2003; Koenigs et al., 2007; Koenigs and Tranel, 2007; Wang, 2014). The odds ratio represents the change in probability of an event (in this case, a rejection) occurring with a change in condition (fairness, offer origin etc.).

3.3.3 Results

3.3.3.1 Outcome of session one

Figure 3-3A displays the rejection rates at each offer level in the first session, for both the FP and GS condition. In line the with published literature investigating the UG, rejection rates decreased with increasing offer levels (Civai, 2013a; Crockett et al., 2008; Gabay et al., 2014; Güth et al., 1982; Sanfey, 2003).

The GEE method estimates a covariance structure for repeated measurements, and when there is very low variance in responses within a 'cluster' (for example, a participant accepting all fair offers), the method is unable to 'converge' on a covariance structure for that cluster. This renders subsequent parameter estimates unreliable. This was the case for fair and hyper-fair offers in the current analysis, where almost every offer was accepted in both the FP and GS conditions (see Figure 3-3B). In order to investigate the effect of offer origin on

unfair offers, I removed the fair and hyper-fair conditions from the model. This analysis found a statistically significant main effect of offer origin, such that there was a 73% reduction in the probability of rejecting an unfair offer in the GS condition compared the FP condition ($\chi^2_{(1,16)} = 11.83$, OR = 0.27, $p < 0.001$). No main effect of gender, or a gender by offer origin interaction was found (*p*s > 0.391).

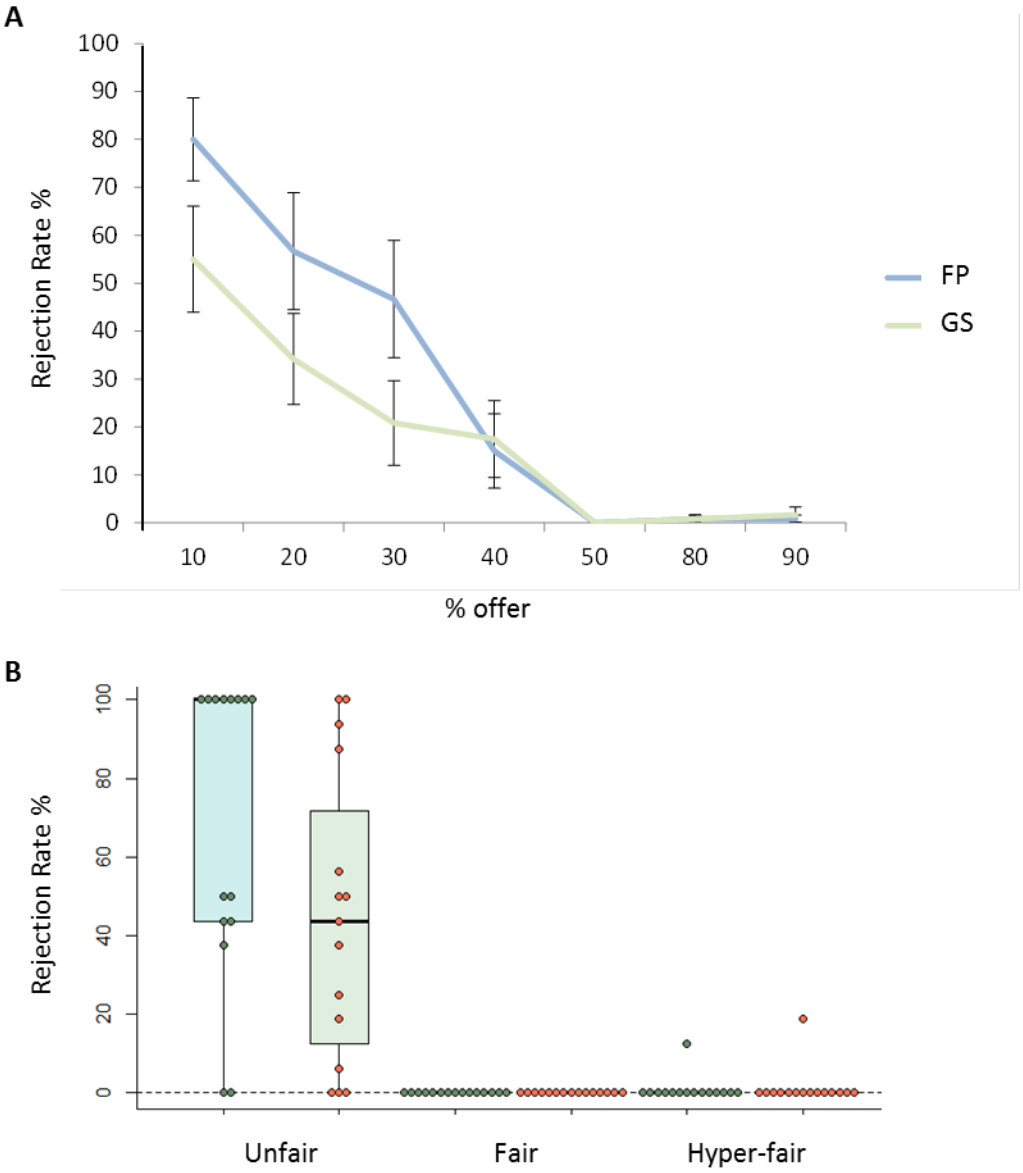


Figure 3-3: Rejection rates from session one of the validation study of the psilocybin study's version of the Ultimatum Game. A) Rejection rates per offer, error bars: ±1SE; FP: First person condition, GS: Random number generator; B) Rejection rates when grouped into unfair (10-20%), fair, (50%) and hyper-fair (80-90%) offers. Boxes represent the interquartile range, with a bold line at the median. Whiskers extend to data points within the range*interquartile range. Individual points are represented by dots. Green dots: FP; orange dots: GS.

3.3.3.2 Test-retest reliability between sessions

Table 3-2 shows the Repeatability (R) estimates and their 95% confidence interval (CI) for each fairness level in each condition.

Generalized mixed models attempt to estimate a covariance matrix of repeated measurements. When there is little variation in response, this is not possible, resulting in a failure to 'converge' on a covariance matrix. In the current data, there was not enough variation in responses in either condition for the fair and hyper-fair offers to calculate a repeatability statistic. Examination of Figure 3-4B and C shows that all but one participant rejected an equal number of offers in each session at these fairness levels, representing almost perfect repeatability.

Table 3-2 shows that responses to unfair offers in both conditions were reliable, with the FP condition showing very high reliability (FP: *R* = 0.82, 95% CIs: 0.56 – 0.97; GS: *R* = 0.69, 95% CIs: 0.39 – 0.86). Figure 3-4A shows the variability in response to unfair offers for each participant. The median change in rejection rates was zero for both conditions, the inter-quartile range being 9.38 and 28.13 for the FP and GS conditions respectively.

Table 3-2: Repeatability (R) estimates with 95% CIs in brackets for each condition across fairness levels. NV = Not enough variation: almost all participants accepted all offers in both sessions

Condition	Fairness Level		
	Unfair	**Fair**	**Hyper-fair**
FP	0.82 (0.56 – 0.97)	NV	NV
GS	0.69 (0.39 – 0.86)	NV	NV

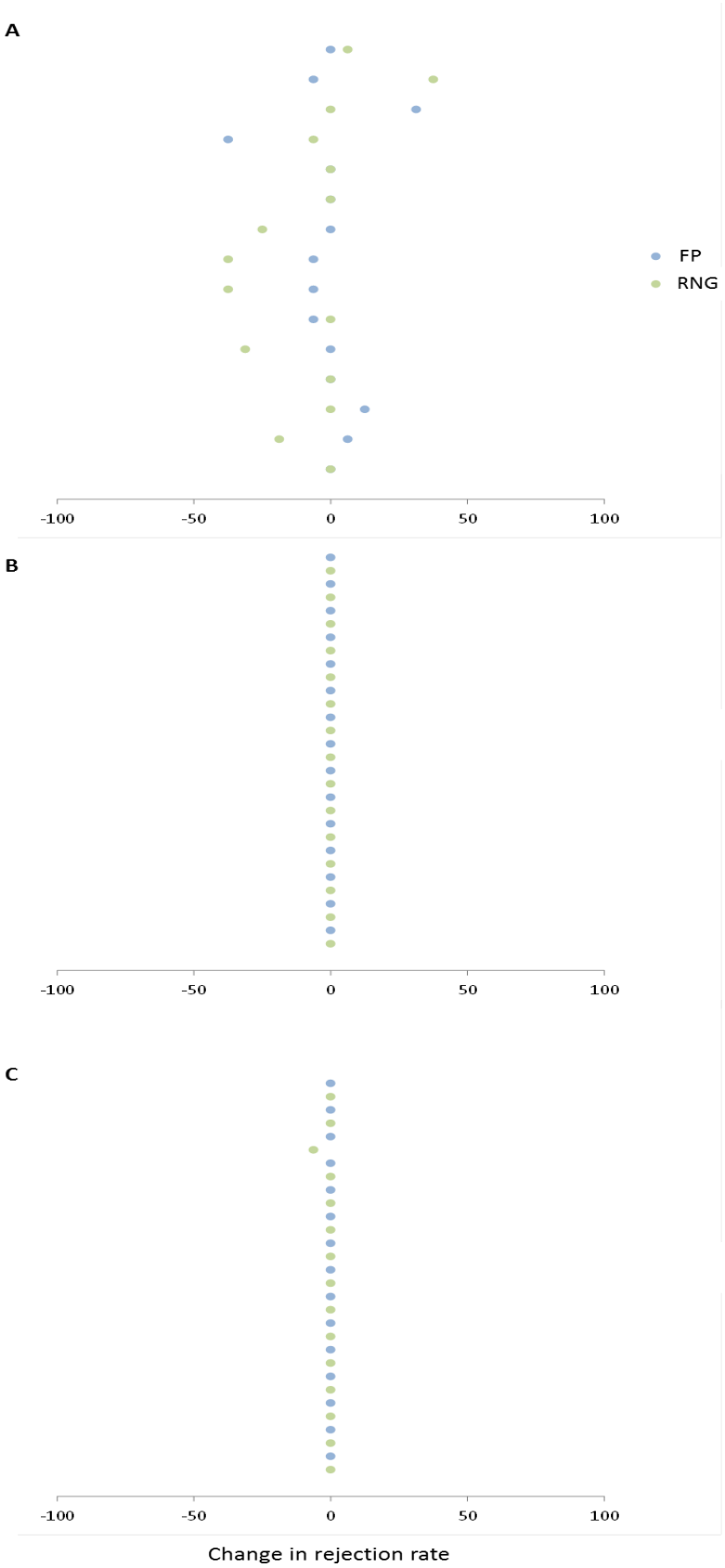


Figure 3-4: Change in rejection rate for each participant in each condition across fairness levels. A) Unfair; B) Fair; C) Hyper-fair

3.3.4 Discussion

This study was designed to investigate the validity of the version of the Ultimatum Game (UG) used in the psilocybin study. Rejection rates to all offer levels showed good test-retest reliability, in both the social and non-social control conditions. Furthermore, the results from session one are in line with those seen in the UG literature.

Taking the first session as an example, the results found in the current version of the task followed the same pattern as those seen in the literature, with decreasing rejection rates with increasing offer levels. Furthermore, there was a difference in rejection rates of low offers when received from a non-social bargaining partner compared to a social partner. It should be noted, however, that the rejection rates seen in the non-social condition were higher than typically seen. For example, in the first neuroimaging study of the UG, the mean rejection rate of 10% offers in the non-social control condition were 35%, compared to 55% seen here. Despite the higher rejection rates of the GS condition, there is still a statistical difference, with a moderate effect size, between the two conditions. This is important as it shows the cognitive mechanisms under investigation in the social condition are in fact due to the social factors of the task rather than purely monetary considerations.

With the evidence that these findings show good test-retest reliability, we do not expect there will be a limited sensitivity to detect changes across multiple sessions, and we can be confident that the effect size detectable by a within-participant study design will not be unnecessarily inflated.

This validation study therefore establishes the current version of the Ultimatum Game as an acceptable protocol, with good test-retest reliability, for use in repeated-measures psychopharmacological studies.

3.4 The effect of psilocybin on social cognition

3.4.1 Abstract

Psilocybin is a compound which causes potent changes in subjective conscious experience. There is strong evidence that these effects are mediated by agonism at the serotonin (5-HT) 2A or 1A receptors. With the serotonergic system implicated in many aspects of social cognition and social decision-making, we investigated the effect of psilocybin on the Ultimatum Game (UG) and facial affect recognition. Furthermore, we administered the src-kinase inhibitor, saracatinib, to investigate whether disruption of putative intracellular pathways related to psilocybin would attenuate any effects seen in these tasks. Twenty male participants completed this study. The effect of psilocybin was compared to a drug-free session in an open-label design, while the effect of saracatinib on psilocybin was tested in a placebo-controlled, crossover design. Thus the tasks were completed on three occasions: drug free, psilocybin alone (Psilo), psilocybin following pre-treatment with saracatinib (Psilo+). Task free functional neuroimaging data were collected on both psilocybin sessions. In the UG, compared to the drug-free session, there was reduced rejection of unfair offers in the Psilo session ($\chi^2_{(1,18)}$ = 4.58, *OR* = 0.42, *p* = 0.006). Compared to the Psilo session, there was an increase in rejection of unfair offers in the Psilo+ session ($\chi^2_{(1,18)}$ = 4.54, *OR* = 1.53, *p* = 0.032). There was no statistical difference in rejection behaviour between the drug-free session and the Psilo+ session ($\chi^2_{(1,18)}$ = 2.26, p = 0.133). There was no difference in facial affect recognition across sessions. An exploratory analysis found differences in functional connectivity related to later UG behavioural changes, and these are

discussed. These data provide evidence that the mixed serotonergic agonist, psilocybin, affects how people respond to violations of social norms in the context of the UG.

3.4.2 Introduction

Section 3.2 introduced the background to the study presented here. It is clear from the literature that the serotonergic system plays an important role in mediating social cognition, including social decision-making (for a review, see Crockett, 2009), with research suggesting that acute administration of a selective serotonin reuptake inhibitor can reduce rejection rates in the Ultimatum Game (UG) (Crockett et al., 2008; M. J. Crockett et al., 2013). Furthermore, psilocybin has been shown to alter emotion processing (Bernasconi et al., 2014; Kometer et al., 2012) and a recent study has examined the sociocognitive effects of psilocybin using a social exclusion paradigm (Preller et al., 2016).

Psilocybin and its metabolite psilocin are potent, mixed serotonergic agonists, with their effects largely the result of its activation of the serotonin 2A (5-HT2A) receptor (Nichols, 2004; for an in-depth discussion psilocybin pharmacology, see 0, Section 1.8.2). Furthermore, evidence from rodent studies suggest the src family of tyrosine kinases are involved in the downstream mechanisms responsible for the psychedelic effects of psilocybin (González-Maeso et al., 2007; Gonzalez-Maeso and Sealfon, 2009).

Saracatinib is an investigational compound which potently inhibits tyrosine kinases, including the src family of kinases (Nygaard et al., 2015). The current study was a mechanistic study with the aim of determining whether saracatinib would alter the behavioural effects of psilocybin in healthy human volunteers. In addition, we investigated whether or not changes in task-free functional connectivity, compared across experimental sessions, of brain regions identified in 0 (Gabay et al., 2014) could be linked to changes in UG behaviour.

We hypothesised that psilocybin would reduce rejection rates of unfair offers in the UG, and that pre-treatment with saracatinib would attenuate this effect. Furthermore, we hypothesised that psilocybin would reduce recognition of negative facial expressions, increase recognition of positive facial expressions, and that pre-treatment with saracatinib would reverse this effect.

3.4.3 Methods

3.4.3.1 Participants

Twenty-three male participants were recruited from the community and gave written informed consent to take part in the study and were financially compensated for their time. Psychopharmacological studies are particularly sensitive to differences in hormone levels in participants. As such, single-sex studies have more power to detect a given effect. Fluctuations in levels of hormones in males are less than those in females, thus making it simpler to choose an all-male design. In addition, there is no information available on the effects of psilocybin and saracatinib on the developing foetus. The sample size

was based on a power calculation relating to imaging parameters not reported in this thesis (arterial spin labelling), and was based on previous psilocybin neuroimaging research (Carhart-Harris et al., 2012). The study received ethical approval from King's College London's Psychiatry, Nursing and Midwifery Research Ethics Committee (PNM/14/15-11).

Exclusion criteria included: personal history of psychiatric illness (assessed with the Mini-International Neuropsychiatric Interview, Sheehan et al., 1998); first-order relative with a history of psychotic illness; evidence of cardiac (assessed with ECG), hepatic, renal, gastrointestinal (assessed with standard blood screening) or neurological disorders; excessive use of caffeine (> six cups of coffee per day) and alcohol (> 28 units per week); current use of medication; failure of drugs of abuse test at screening or on either study day (drugs tested for: amphetamine, barbiturates, benozodiazepines, cocaine, THC, methadone, methamphetamine, opiate, phenylcyclidine, tricyclic antidepressants). Participants were only included in this study if they had at least one previous experience with a hallucinogenic drug. Participants were excluded if any previous experience could be described as 'negative', or a 'bad trip'. We did not collect data on lifetime use.

Three participants did not complete the study: the QTc reading of one participant's ECG exceeded the upper limit specified in the study protocol on the day of testing; one participant experienced high anxiety prior to the psilocybin dosing on his first session and withdrew from the study (following unblinding it was revealed he had taken placebo on this session) and one participant tested positive for cocaine on the morning of his second session. As

such, 20 participants completed the study (mean age 26.6, SD 7.1, range 19 – 47).

3.4.3.2 Experimental procedure

This study followed a double-blind, placebo-controlled, cross-over, counter-balanced design. Following a successful screening, participants attended two experimental study days at least one week apart (mean 13.3 days, SD 3.5, range 1 – 15). On each experimental study day participants would receive a placebo followed by psilocybin (“Psilo”) or saracatinib followed by psilocybin (“Psilo+”).

See Figure 3-5 for a schematic representing the study day. Participants arrived at the study centre at 08:30, at which time we repeated neurological, cardiac, and general health safety checks to ensure nothing had changed since their screening visit. At 10:00 participants were dosed with either 125mg saracatinib or placebo, orally. At 30 minutes and 120 minutes post-dose participants gave a blood sample. At 180 minutes post-dose participants completed some questionnaires and were retrained in the tasked they were to perform in the scanner. At 240 minutes post-dose participants entered the scanner. The scanning session lasted 90 minutes, with an infusion of 2mg psilocybin over 2 minutes occurring approximately 40 minutes into the scanning session (280 minutes post saracatinib).

Following the scanning session, a further blood sample was taken and participants completed a questionnaire of subjective effects, the UG (340 minutes post saracatinib) and the Affective Bias task (355 minutes post

saracatinib). Participants then completed further questionnaires before commencing discharge procedures. The study typically finished at around 17:00. For the current chapter only the results of the UG and Affective Bias task will be considered. Analyses of blood samples collected during this study are not reported in this thesis, due to the data not being available at the time of writing.

For full details of the UG task implemented in this study see Section 3.3, which outlines the stimuli and trial duration. Appendix B presents the task instructions used for this task. . Briefly, participants were told they would receive offers out of £20 from either another player whose offer had been collected as part of another study (FP) or a randomly computer generated offer (GS). In both cases, acceptance of the offer would lead to the money being split as offered, while rejection would mean that neither player would receive any money for that round. Participants were told they would receive one percent of the amount of money earned during the course of the task; in reality they were paid a fixed sum for participation in the study as a whole. Table 3-1 displays the number of offers at each offer level. In this study participants received offers in two conditions (FP and GS), leading to a total of 96 offer trials presented in one run of the task.

The Affective Bias task was taken from the EMOTICOM cognitive test battery (Bland et al., 2016). In this task participants see a face appear on the screen for approximately half a second and are asked to indicate which emotion the face was expressing from a choice of happy, sad, fear or anger. For each emotion

there are nine levels of intensity. Control conditions of faces of different ages were presented at the half way point in the task.

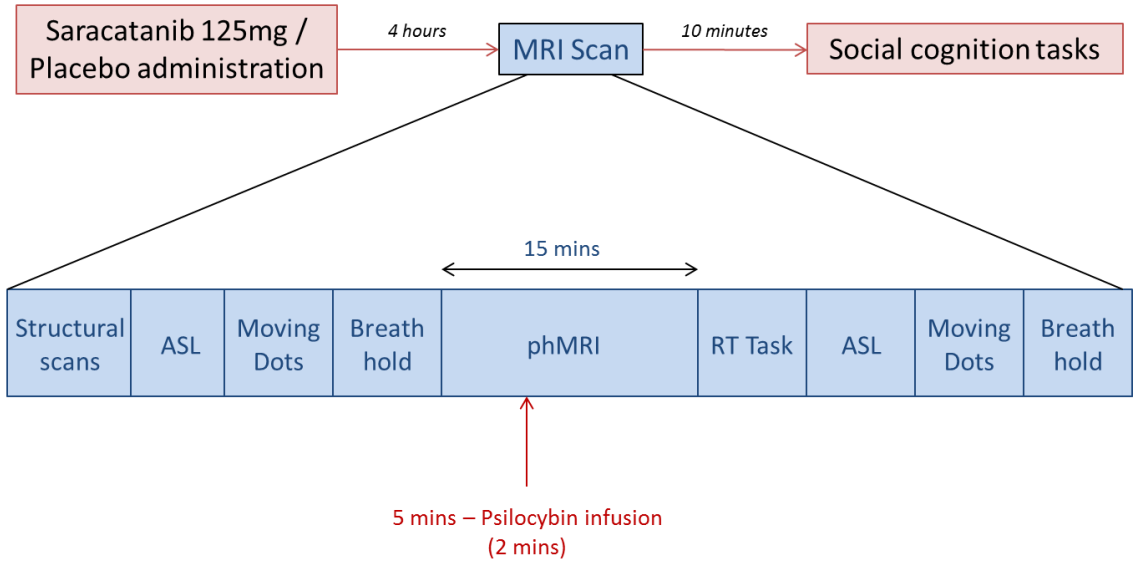


Figure 3-5: Graphical representation of the study day. ASL: arterial spin labelling; Moving dots: visual processing task; phMRI: pharmacological MRI; RT task: reaction time task

3.4.3.3 Statistical analyses

The Ultimatum Game

The data collected was in the form of categorical (accept or reject) responses to monetary offers. Converting this data to proportions and analysing with an ANOVA is problematic on two fronts. First, the proportion data is non-normally distributed. Second, variance of binomial distributions do not show homogeneity, thus violating the assumptions of ANOVA (Jaeger, 2008).

As such, the current data have been analysed using repeated-measures logistic regression, implemented with generalized estimating equations using IBM SPSS Statistics for Windows (IBM Corp., 2012). This is a nonparametric test which takes into account the correlation of responses within subjects, and produces a chi-squared statistic (χ^2), an odds ratio (OR) and its 95% confidence interval (CI), and a *p*-value. It is a recommended approach to analysing categorical data that has been used in a number of studies in the UG literature (M. J. Crockett et al., 2013; Hanley et al., 2003; Koenigs et al., 2007; Koenigs and Tranel, 2007). The odds ratio represents the change in probability of an event (in this case, a rejection) occurring with a change in condition (fairness, offer origin etc.).

Since both experimental sessions involved administration of psilocybin, and the task was administered post scan only, participants were also asked to complete the task at screening, to act as a baseline measure. This is justified, given the test-retest reliability demonstrated in the previous section of this chapter.

Affective Bias

The Affective Bias task has a number of outcome measures. First is the percentage accuracy for each emotion (fear, anger, happy, sad) and control condition. Secondly is the affective bias, defined by Bland and colleagues (Bland et al., 2016) as the difference between happy and sad emotion accuracy. Finally, one can consider the bias of incorrect responses – i.e. what proportion of wrong responses corresponded to each emotion.

Here, we will compare these outcomes across sessions using repeated measures ANOVA, following up with post-hoc pairwise comparisons where appropriate. As with the UG, this task was administered post-psilocybin on both study days, so participants completed this task at the drug-free screening to act as a baseline measure.

3.4.3.4 MRI data acquisition and analysis

Functional images were acquired with a MR750 3.0 Tesla (T) General Electric MR scanner using a 32-channel head coil. A T2*-weighted echo-planar imaging sequence was used, with the following parameters: TR: 2500 ms; Multi-echo TEs: 12, 28, 44, 60ms; flip angle: 80°; slice thickness: 3.2 mm; field of view: 240; number of slices: 28; 356 time points. We also acquired a structural Magnetization Prepared Rapid Gradient Echo (MPRAGE) image with the following parameters: TR: 7312 ms; TE: 3.02 ms; flip angle 11°; slice thickness: 12 mm; 196 sagittal slices; field of view = 270.

Multi-echo image acquisition acquires data at multiple echo times for each slice. This allows better characterisation of the BOLD-response, enabling an independent component analysis (ICA) to differentiate non-BOLD noise signal from BOLD-related signal changes. This method is described below. Multi-echo data pre-processing was performed using the AFNI (Cox, 1996) tool *meica.py* (Kundu et al., 2013, 2014). Pre-processing steps included six-parameter rigid body motion correction, time-series de-spiking and slice time correction. Functional data were then optimally combined (OC) by taking a weighted summation of the four echoes, using an exponential T2* weighting approach (Posse et al., 1999).

The OC data were then de-noised with the AFNI tool *meica.py* (Kundu et al., 2013, 2014). Multi-echo principal components analysis was first applied to the OC dataset to reduce the data dimensionality. Spatial ICA was then applied and the independent component time-series were fit to the pre-processed time-series from each of the four echoes to generate ICA weights for each echo. These weights were then fit to the linear TE-dependence and TE-independence models to generate F-statistics and component-level κ and ρ values, which respectively indicate BOLD and non-BOLD weightings. The κ and ρ metrics were then used to identify the non-BOLD-like components to be regressed out from fMRI data. Further technical details on ME-ICA can be found in (Kundu et al., 2015).

After de-noising, data were spatially smoothed with an 8-mm full width at half maximum Gaussian kernel and high-pass temporal filtered with a cut-off frequency of 0.005 Hz.

A study-specific template representing the average T1-weighted anatomical image across subjects was built using the Advanced Normalization Tools (ANTs) (Avants et al., 2011) toolbox. Each participant's cleaned dataset was co-registered to its corresponding structural scan, then normalized to the study-specific template before warping to standard MNI152 space, with $2\times2\times2mm^3$ resampling.

The resting state scan was 15 minutes long. Participants were instructed to keep their eyes open and look at a fixation cross. Five minutes into the scan participants were infused with 2mg psilocybin, dissolved in 5ml saline solution, at a steady rate over a period of two minutes. Previous research from our group

has investigated the pharmacological MRI response to drug infusions by modelling a gamma variate regressor at the first level (De Simoni et al., 2013; Doyle et al., 2013). The gamma variate response function was based on the following equation:

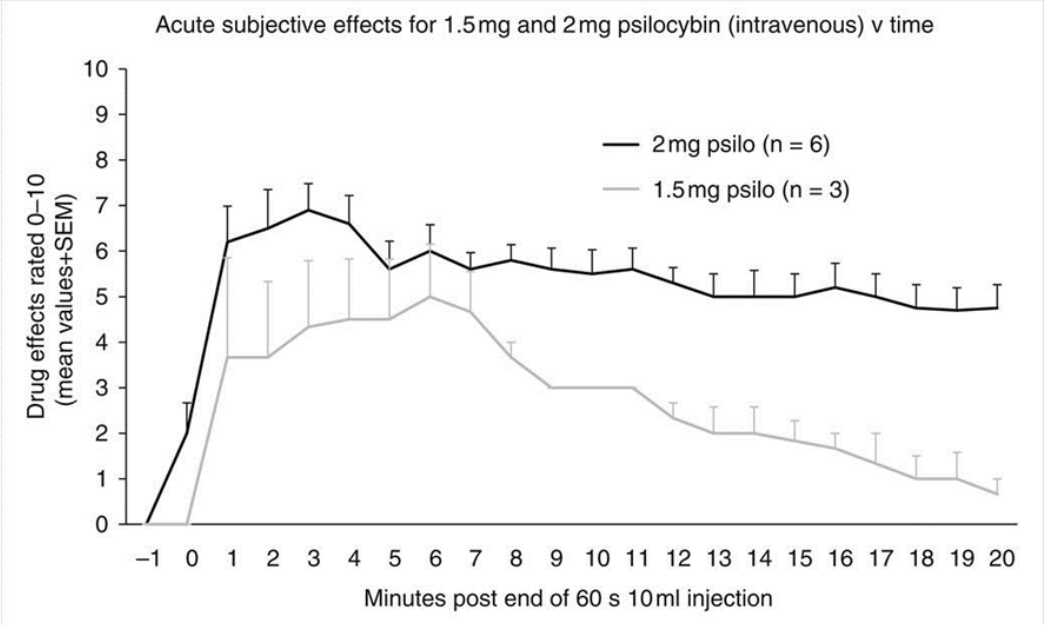
$$f(t) = \left(\frac{t}{t_{max}}\right)^{t_{max}\beta} e^{(t_{max}-t)\beta}$$

where t_{max} is the time of peak amplitude and β is a shape parameter. In the current study I was interested in modelling the subjective effects of the psilocybin infusion. A study from Carhart-Harris et al (2011) had participants rate the intensity of the subjective effects, every minute for 20 minutes, of an intravenous infusion of psilocybin at the same dose used in the current study. It should be noted however, that those authors infused the participants over one minute rather than two minutes. Figure 3-6A is taken from that publication and displays these subjective ratings. Here it can be seen that the peak effects are reached approximately three minutes from the end of the infusion. For the gamma variate function used in the current analysis, t_{max} was set to 96 (96 volumes = 4 minutes from the middle of the infusion) and the shape parameter was adjusted to fit the rate of decline in the subjective effects seen in Figure 3-6, set at 0.004. The gamma variate first level covariate was padded with zeros at its start, up until the time of infusion.

All connectivity analyses were carried using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). By modelling this function as part of a GLM at the first level, this analysis attempts to examine how functional connectivity changes in line with the expected subjective effects (see Figure 3-6B). I carried

out a seed-to-voxel bivariate correlation analysis using the peak voxels from five clusters identified in the meta-analysis reported in 0 (Gabay et al., 2014, see Figure 3-7). These seeds were: anterior cingulate gyrus (ACCg; MNI 6, 10, 30); right anterior insula (MNI 40, 11, 10); left frontal operculum/anterior insula (MNI -42, 13, 8); left fusiform gyrus (MNI -26, -73, -4); right cerebellum, cruss1 (MNI 26, -71, -34). At the second level, the experimental sessions were contrasted, to identify regions whose connectivity with these seeds was different between the Psilo and Psilo+ sessions. To control for multiple comparisons, an F-contrasts was carried out looking for any effect of seed. Follow-up comparisons were carried out where appropriate. Following this, a second-level covariate was included in the model. This looked for regions whose connectivity with the seeds co-varied as a function of the participants change in rejection behaviour in the UG. I acknowledge the time delay between the scan and completing this task. However, since the gamma variate function attempted to capture the change in connectivity related to changes in subjective effects of the drug over time, this exploratory analysis could still be informative about possible mechanisms underlying the UG.

A



B

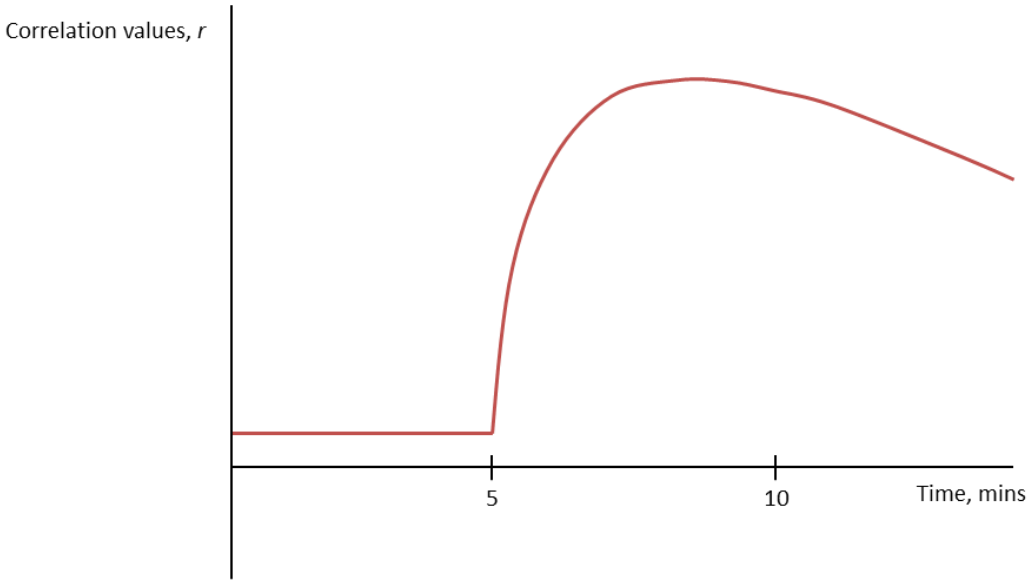


Figure 3-6: A) Reproduced from Carhart-Harris (2011): "The 0–10 ratings were anchored with 0 being 'no noticeable drug effects' and 10 being 'extremely intense effects'. Time zero corresponds to the end of the 60 s injection" B) Gamma variate function. The connectivity analysis looked for changes in connectivity values which fit this function

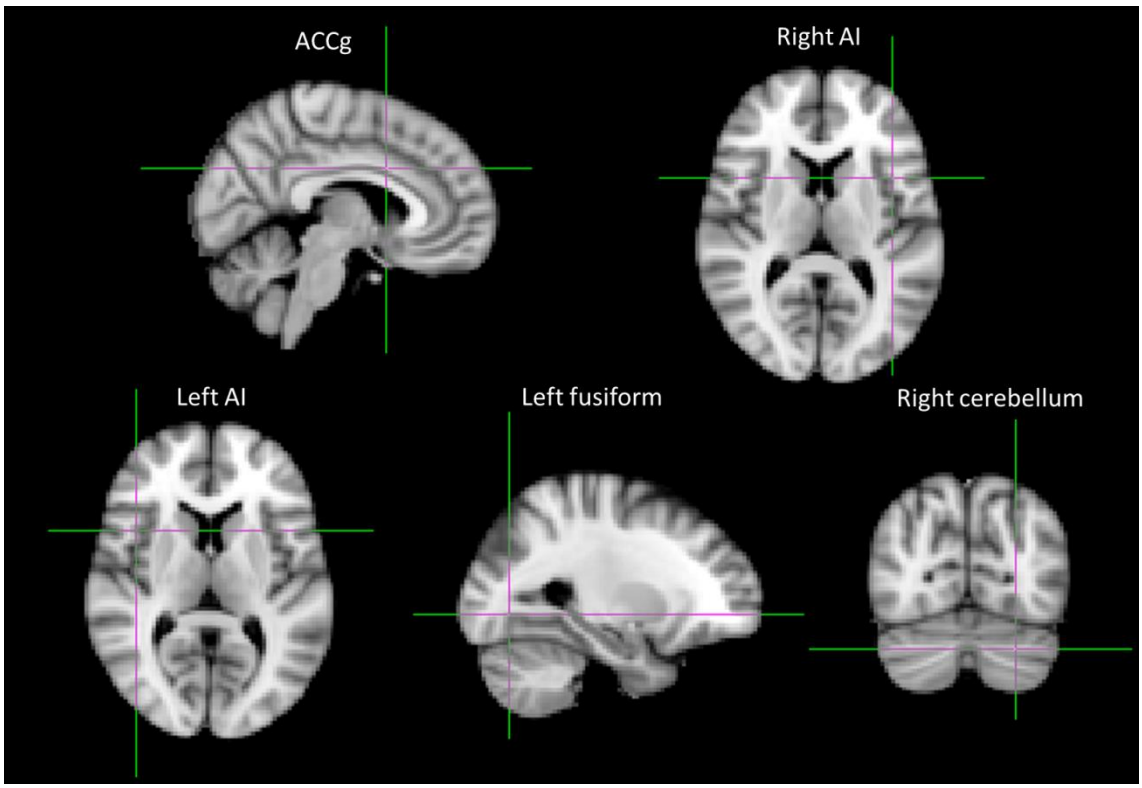


Figure 3-7: Seeds used in the connectivity analysis. ACCg: anterior cingulate gyrus (MNI 6, 10, 30); AI: anterior insula (right MNI 40, 11, 10; left MNI -42, 13, 8); left fusiform MNI -26, -73, -4; right cerebellum MNI 26, -71, -34.

3.4.4 Results

3.4.4.1 Ultimatum Game

Due to technical issues, one participant's responses were not recorded in the Psilo+ session. In this section we will mostly consider responses to unfair offers. For the other offer levels, the results are briefly summarised here: With the exception of one participant in the Psilo session and three participants in the Psilo+ session, all fair and hyper-fair offers were accepted. Of those who rejected offers at these fairness levels, one participant rejected 50% and 43.8%

of FP hyper-fair offers and GS hyper-fair offers respectively in the Psilo session. The same participant rejected 56.2% and 18.8% of offers in these same conditions in the Psilo+ session. In addition, one participant rejected 12.5% of fair FP offers in the Psilo+ session, and yet another rejected 6.3% of GS hyper-fair offers in the Psilo+ session.

Figure 3-8 displays a boxplot of rejections rates of unfair offers in the FP and GS conditions across sessions. There was a statistically significant main effect of offer origin, such that, compared to the FP condition, there was a reduced probability of rejecting unfair offers in the GS condition ($\chi^2_{(1,18)}$ = 6.24, *OR* = 0.49, *p* = 0.013). Compared to the screening session, there was a statistically significant reduction in the probability of rejecting FP unfair offers in the Psilo session ($\chi^2_{(1,18)}$ = 4.58, *OR* = 0.42, *p* = 0.006). Compared to the Psilo session, there was a statistically significant increase in probability of rejecting FP unfair offers in the Psilo+ session ($\chi^2_{(1,18)}$ = 4.54, *OR* = 1.53, *p* = 0.032). There was no statistical difference in FP unfair rejection behaviour between the drug-free screening session and the Psilo+ session ($\chi^2_{(1,18)}$ = 2.26, p = 0.133).

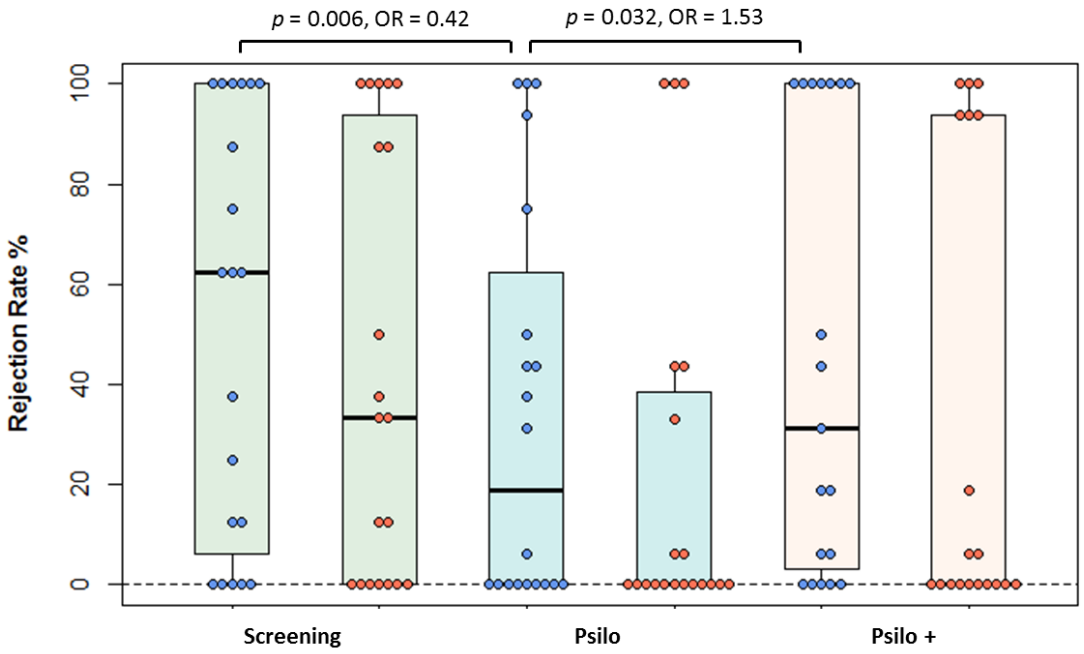


Figure 3-8: Boxplot displaying rejection rates of unfair offers in the Ultimatum Game across conditions. *OR*: odds ratio. Blue dots: FP condition; Orange dots: GS condition

3.4.4.2 Affective Bias

Three participants did not complete the task at screening. One participant was unable to complete all assessments due to time restrictions and for two there were technical difficulties with the computer equipment. As such, all analyses presented here are based on N = 17. Figure 3-9A displays the mean number of correct responses for both the control faces and all emotions pooled together. A 2x3 repeated-measures ANOVA revealed that participants showed greater accuracy in the control condition than the affective condition across sessions ($F_{(2,16)}$ = 7.647, p = 0.014, $\acute{\eta}^2$ = 0.323). There was no statistically significant

change in accuracy in either condition across sessions ($F_{(2,32)}$ = 0.534, p = 0.572, $\acute{\eta}^2$ = 0.032).

A one-way ANOVA revealed that Affective Bias, the difference between accuracy of happy and sad emotion identification, showed no statistical difference across sessions (see Figure 3-9B; $F_{(2,32)}$ = 1.019, p = 0.370, $\acute{\eta}^2$ = 0.060). Furthermore, of those emotions identified incorrectly, there was no change in bias in the responses incorrectly given (see Figure 3-9C; $F_{(2,32)}$ < 0.001, p = 1).

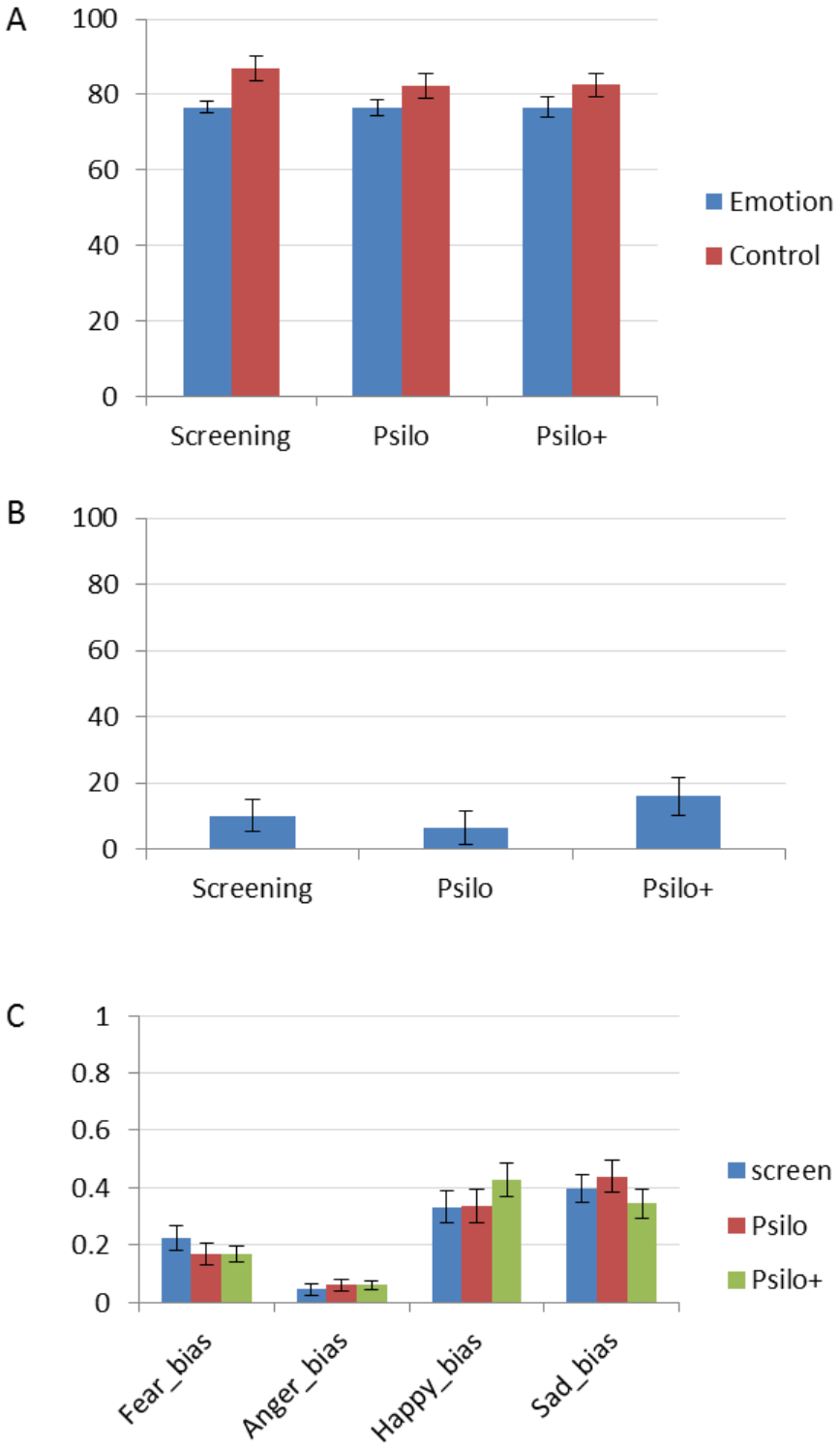


Figure 3-9: Affective Bias results. A) Comparison of accuracies of affective and control conditions, B) Affective bias (proportion of happy correct minus sad correct, C) Bias of wrong responses i.e. when given an incorrect answer, what was chosen. All error bars: +/- 1 SE

3.4.4.3 Subjective effects

In this study, participants were asked to complete a subjective effects visual analogue scale questionnaire obtained from the authors of Carhart-Harris et al (2011). The first question on this questionnaire was “How intense were the drug effects when at their peak”. There was a statistically significant reduction in reported intensity during the Psilo+ session compared to Psilo session ($t_{(17)}$ = 1.99, one-sided p = 0.031; two participants did not answer this first question on one session).

In order to assess whether changes in UG rejection behaviour can be explained by changes in the overall subjective effects of the drug, I carried out a regression analysis with subjective rating of peak intensity as the independent variable and rejection of unfair FP offers as the dependent variable. There was no statistically significant relationship between the two variables (Beta = 0.175, p = 0.502).

3.4.4.4 Exploratory functional connectivity analysis

Figure 3-10 and Table 3-4 display the results from the functional connectivity analysis carried out on the pharmacological MRI data. This analysis used a first level covariate to identify how the seeds’ connectivity changed in line with the subjective effects.

Carrying out an F-contrast to look for any changes across all seeds, three clusters were identified: left lateral occipital cortex; right central opercular/posterior insular, extending to mid/anterior insula; left cerebellum, anterior lobe. Examination of the beta estimates for this analysis suggests that

there was greater connectivity between the left fusiform seed and the occipital cluster during the Psilo session than during the Psilo+ session, and that both the ACCg and left fusiform seeds showed increased connectivity with the insula cluster, and that the fusiform, ACCg, and right insula seeds showed increased connectivity with the cerebellar cluster, during the Psilo session compared to the Psilo+ session.

Including a second level covariate of change in rejection rate of unfair UG offers between sessions, one cluster was identified in the right orbitofrontal cortex. Examining the beta estimates for this analysis suggests a significant correlation between change in rejection rates and the connectivity of the right anterior insula to this orbitofrontal cluster, and connectivity of the left fusiform gyrus to this orbitofrontal cluster ; such that the greater the increase in connectivity, the greater the increase in rejection rate from the Psilo to Psilo+ condition.

Table 3-4:Clusters showing changes in functional connectivity across experimental sessions

Cluster level			Peak level				
Region	FDR-corr *p*-value	Cluster size	MNI *x*	MNI *y*	MNI *z*	*z*-value	
F-contrast contrast of changes from Psilo to Psilo+							
Left Lateral occipital cortex	0.002	349	-34	-86	10	4.70	
Right central operculum/ posterior insula	0.002	323	58	0	6	4.08	Central oper/ post insula
			38	8	8		Mid/ant insula
Right cerebellum, anterior lobe	0.002	377	-26	-46	-28	3.82	
F-contrast contrast of changes from Psilo to Psilo+, with a second level covariate of change in rejection rates of unfair offers between these two sessions							
Right orbitofrontal cortex	0.019	321	24	36	-12	4.17	
			28	24	0	3.67	

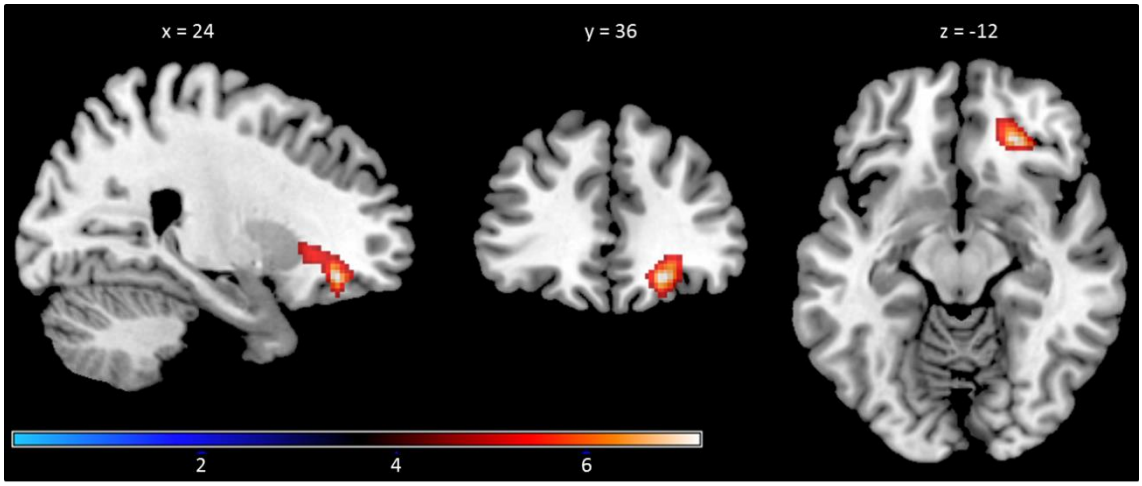


Figure 3-10: OFC cluster whose change in connectivity with the right anterior insula and left fusiform gyrus covaried with change in rejection rate across sessions

3.4.5 Discussion

This study is the first to provide direct evidence of specific serotonergic receptor involvement in behaviour underlying responses to unfair offers in the Ultimatum Game (UG). As hypothesised, when responding to UG offers following intravenous administration of psilocybin – at a point where the most acute drug effects had diminished – participants showed a reduced probability of rejecting low offers compared to the drug-free screening visit. Treatment with the src-family kinase inhibitor, saracatinib, appears to attenuate this effect. Furthermore, an exploratory analysis revealed a statistically significant relationship between changes in rejection rates across experimental sessions and the functional connectivity between a cluster in the right orbitofrontal cortex (OFC) and both the right anterior insula and left fusiform gyrus, in task-free functional neuroimaging during the period of the acute drug effects. Counter to our hypothesis, there was no change in facial affect recognition across sessions.

Studies have previously implicated the serotonergic system in responses to unfairness in the UG (Crockett et al., 2008; M. J. Crockett et al., 2010, 2013). These studies found that altering serotonin availability through SSRI administration and tryptophan depletion (ATD) altered rejection rates of moderately unfair offers, but not very unfair offers (10-20%). The current study extends these findings by providing evidence of changes in rejection behaviour for the most unfair of offers. The authors of the previous studies claim that reduced rejection is due to an increased harm aversion being induced by greater serotonin availability, and that rejecting an offer harms the other by

denying them reward (M. J. Crockett et al., 2010). There is of course the harm to oneself implicit in rejection behaviour – by rejecting an offer one forgoes one's own financial reward. Indeed, this is what makes rejection behaviour in the UG so interesting. When people reject unfair offers, one's own loss is considerably lower than that of the proposer, and it is considered a prosocial act to forgo this reward in the interest of punishing a violation of social norms (Fehr and Fischbacher, 2003).

In this light, it is possible to consider a decrease in rejection as being due to a change in reward sensitivity, or an increase in loss aversion. A limitation of the current study is that neither of these possibilities were explored. However, Crockett et al (2015) specifically included loss aversion in a computational model of 'moral' decision-making and found no change as a result of serotonergic manipulation. Furthermore, Takahashi (2012) conducted a review of monoamine influence on risk during (non-social) decision-making and concluded that increased serotonergic activity would lessen, rather than increase loss aversion.

A study investigating the effect of training in mindfulness meditation on UG behaviour found similar results to those presented here, such that participants accepted more unfair offers post training (Kirk et al., 2016). Drawing on the finding that accompanying this decrease in rejection rate was an attenuation of anterior insula activation in response to unfair offers, the authors of this study claimed that the change in behaviour may be due to greater emotion regulation. This draws on the hypothesis that rejection behaviour is driven by a negative emotional reaction to unfair treatment (e.g. Sanfey, 2003), and that regulation of

this then led to greater social cooperation. The current study did not include any measurement of emotional states, so it is not possible to speculate too far on the psychological mechanisms underlying the changes in UG behaviour seen here.

In an important extension of previous psychopharmacological studies of UG behaviour, the current study has shown the serotonergic effect to be specific to particular receptor subtypes, through use of a preferential 5-HT1A/2A receptor agonist (Passie et al., 2002). SSRIs and ATD cause global changes to serotonergic availability; the first through inhibition of presynaptic reuptake, the latter through limitation of serotonin precursor compounds (Stahl, 2013; Young, 2013). Changes in behaviour following either manipulation cannot provide specific insight into the serotonergic mechanisms underlying these changes. Psilocybin acts with highest affinity at 5-HT1A and 5-HT2A receptors (Passie et al., 2002), and there is evidence to suggest that conformational changes following hallucinogen binding at these receptors activate additional intracellular, second-messenger pathways (González-Maeso et al., 2007; Gonzalez-Maeso and Sealfon, 2009). This same evidence suggests that one of these pathways relies on the src-family kinases. By attenuating the effect of psilocybin on UG behaviour through inhibition of src-kinase, we have provided dual evidence that the behavioural changes presented here are due to 5-HT1A/2A agonism.

A motivation for the current study was the current lack of research examining the psychopharmacology of social decision-making. However, there is evidence of 5-HT2A receptor involvement in other aspects of social behaviour. In a study

investigating the effects of psilocybin, the 5-HT2A receptor antagonist ketanserin blocked drug-induced reductions in recognition of negative facial affect (Kometer et al., 2012). In mice, increases in social behaviour, following administration of 3,4-methylenedioxy-methamphetamine (MDMA), were linked to 5-HT1A receptors (Thompson et al., 2007). Also in mice, there is some evidence that effects of the cannabinoid THC on social interaction are reliant on 5-HT2A receptors (Viñals et al., 2015). The current finding that the 5-HT1A/2A receptor subtypes play a crucial role in rejection behaviour in the UG extends these findings to human interpersonal interactions.

In this study we have also shown a relationship between changes in functional connectivity during the acute phase of the psilocybin effect with behaviour in the UG after the psychedelic effect has largely dissipated. These changes were seen in the connectivity of voxels of interest identified in the meta-analysis of UG neuroimaging studies reported in 0 (Gabay et al., 2014). Whilst acknowledging the time delay separating collection of these data (approximately 50 minutes), and the vast differences between the acute psilocybin effects and those still being experienced at the time of UG data collection, these data provide preliminary evidence that changes in connectivity, mediated by 5-HT1A/2A receptor activity, can influence behaviour in interpersonal interactions.

By using a gamma variate model based on the trajectory of subjective effects measured by Carhart-Harris et al (2011), the connectivity findings examine changes that follow this trajectory. Follow-up studies should attempt to replicate these findings, which are discussed below, whilst completing the task during functional neuroimaging. A benefit of the current design is that UG behaviour

was not confounded by the profound alterations in experience induced by psilocybin administration. Unfortunately we do not have subjective effects data from the time of completing the UG task, but we did not find a relationship between changes in the peak effects and UG behaviour across sessions. The current findings could inform analysis design in fMRI-UG studies investigating other serotonergic compounds.

When looking at changes in seed connectivity across experimental conditions, the left fusiform gyrus and ACC_g seeds showed increased connectivity to a cluster which encompassed the right anterior insula, and right central operculum/posterior insula region during the Psilo compared to Psilo+ session. There is growing evidence that the ACC_g is involved in tracking others' motivations during interpersonal interactions (M. A. J. Apps et al., 2013; Apps et al., 2016; Apps and Sallet, 2017). There is strong evidence that the anterior insula is involved in responses to norm violations, be it to signal negative emotions associated which such violations or inequality more generally (Civai et al., 2012a; Civai, 2013a; Sanfey, 2003; Sanfey et al., 2014). If one can extrapolate that these changes in connectivity may still be present at the time of UG completion, these results suggests that a greater integration of these regions may play a role in driving rejection behaviour. Furthermore, the central operculum/posterior insula region has been implicated in UG studies, particularly in reference to accepting unfair offers (Güroğlu et al., 2011b; Kirk et al., 2011b, 2016). In the current study, acceptance of unfair offers was seen more often in the session with higher connectivity of this region to the ACC_g.

This is an intriguing finding which should be followed up with a study which collects UG and imaging data concurrently.

The current findings also suggest that the connectivity between the right anterior insula and the OFC varied in line with changes in rejection rate across experimental sessions; participants whose rejection rates increased more from the Psilo to Psilo+ session showing greater increase in the connectivity of these regions. The OFC has been implicated in reward processing across a range of domains, including in the UG (e.g. Becker et al..; Domenech et al.; Howard and Kahnt, 2017; Tabibnia et al., 2008). The finding that connectivity between the anterior insula, which is involved in signalling norm violations, and the OFC was altered in line with the magnitude of change in rejection rates suggests some role for the integration of these two processes in UG responder behaviour. Again, this hypothesis needs to be explicitly followed up with fMRI data collected during the UG itself.

It is surprising that no changes were found across experimental sessions for the Affective Bias task. Studies investigating the effect of SSRIs have found changes in emotion recognition, albeit with some conflicting results (e.g. Alves-Neto et al., 2010; Browning et al., 2007; Capitão et al., 2015; Harmer et al., 2003a). One interpretation of the current study is that it may be evidence that the findings in previous studies are not due to 5-HT1A/2A receptor activity, but some other serotonergic effect. The Affective Bias task was not performed during the acute effects of psilocybin, which occurred while the participants were still in the scanner, but at a time where the subjective effects were very much reduced. Previous studies administering psilocybin during its acute stage

have demonstrated an effect on emotion recognition (Kometer et al., 2012; Schmidt et al., 2013). Therefore the acute and delayed effects of psilocybin on emotion processing may differ. Establishing this relationship is potentially important, given recent evidence of the antidepressant effects of psilocybin outside of the psychedelic window (Carhart-Harris et al., 2016; Griffiths et al., 2016). The results presented here suggest that the UG may be a more sensitive measure of serotonergic changes in social processing than facial affect recognition.

It could be that the perceptual disturbances of the psychedelic effect itself impaired facial processing in those previous studies (Kometer et al., 2012; Schmidt et al., 2013). Kometer et al (2012) found improved recognition of positive, but not negative valence; Schmid et al (2013) found reduced sensitivity to negative, but not positive, valence. While the acute psychedelic perceptual disturbances would not explain the differential effects of positive vs negative valence, there was no non-emotional control condition. Acute perceptual disturbances would not have been present in the current study precisely because the task was administered later in the time course of the drug effects. The Affective Bias task used in the current study includes a control condition where participants are asked to identify the age-range in which different faces belong (Bland et al., 2016). The fact that decision-making in this context was not altered across sessions shows that these perceptual disturbances were not an issue in the current study.

The study presented here provides evidence of 5-HT1A/2A receptor involvement in responder behaviour in the UG. To follow up on this it would be

beneficial to establish any changes in reward sensitivity and loss aversion in non-social tasks. This would provide a better clarification that these effects are truly due to social processing. Differences were seen here between the social and non-social control condition, and as expected the drug treatment did not alter rejection rates in the non-social control condition. However, given that these were low already, it is feasible that the changes seen were not due to changes in social processing.

Rejection behaviour in the UG is considered to be a prosocial behaviour (Rand et al., 2013; Rilling and Sanfey, 2011; Sanfey, 2003), yet rejection of unfair offers has also been classed as causing another harm, with reduction in rejection rates being an increase in harm aversion (Crockett, 2009). Recent studies have included a third-party condition, where participants make social decisions that do not affect their own outcome (Civai et al., 2012a, 2015; C. Corradi-Dell'Acqua et al., 2013). By including such a condition in future psychopharmacology research, not only could one extend the literature attempting to explain 'non-rational' behaviour in social decision-making tasks, it would also help to tease apart the nuances in serotonergic activity in these tasks.

A limitation of the current study was the open-label design of the psilocybin-drug-free comparison. While placebo-controlled studies are the gold standard for psychopharmacology research, the difficulty in blinding compounds with such profound subjective effects as psilocybin is a recognised challenge for the field. This will be discussed further in Chapter 5. It should be noted that this limitation was not present when testing the effects of saracatinib, as any

subjective effects were subtle and participants were unable to discriminate saracatinib from placebo.

Saracatinib is selective to src-family kinases, which in turn appear to be primarily associated with whose G-protein coupled receptors including the $G_{i/o}$ subunit (Luttrell and Luttrell, 2004; Nygaard et al., 2015). Whilst the hypothesised mechanism being tested in this study was psilocybin-induced 5-HT2A/1A interaction with $G_{i/o}$ subunits, there does exist the possibility that the saracatinib effect seen was due to inhibition of src-signalling from other receptor $G_{i/o}$ subunits. For example, dopamine D2 receptor activation involves this same subunit (British Pharmacological Society, accessed 2017). Therefore it is possible that the saracatinib effect is due to an influence on psilocybin's indirect modulation of dopamine activity, or a psilocybin-independent effect on $G_{i/o}$ signalling.

Conclusion

The study presented in this chapter has provided strong evidence for the role of specific receptor subtypes, the 5-HT1A/2A receptors, in rejection behaviour in the Ultimatum Game, such that agonism at these receptors reduces rejection of unfair offers. Provisionally, there appears to be a relationship to these changes and the connectivity between the anterior insula and orbitofrontal cortex, although these data were collected during an earlier, acute phase of drug effects than the UG data. No changes were seen in facial affect recognition, possibly suggesting different serotonergic mechanisms underlying this aspect of social cognition. Future work should aim to further clarify the neural mechanisms underlying the psychopharmacology of social decision-making.

Chapter 4 The effect of MDMA on social cognition

4.1 Overview

This chapter examines the effects of the 3,4-methylenedioxy-methamphetamine (MDMA) on social decision-making, emotion recognition, and empathy. These were measured using the Ultimatum Game (UG), Prisoner's Dilemma (PD), Affective Bias task and Multifaceted Empathy Test (MET). In addition to behavioural data, functional neuroimaging data was collected for the UG and PD.

Section 4.2 will introduce the study reported in this chapter. Section 4.3 will introduce the versions of the PD and UG[2] used in this study and report on their test-retest reliability. Section 4.4 will then present the method, results and discussion of the study examining the effect of MDMA on social cognition.

[2] One modification was made to this version of the UG before use in the MDMA study, which is detailed in Section 4.4.3.2

4.2 Introduction

Social cognition deficits are increasingly recognised as a fundamental aspect of a range of psychiatric illnesses, and current medications do not effectively treat these deficits (see 0; Gabay et al., 2015; Nuechterlein et al., 2004). 0 provided a detailed overview of these deficits. While deficits in emotion recognition and empathy are quite clearly established across a range of disorders (e.g. Bora and Pantelis, 2013; Dalili et al., 2015; Dziobek et al., 2011, 2008; Kohler et al., 2010; Mazza et al., 2014), the research looking at social decision-making is less clear-cut, with a number of studies finding alterations across psychiatric conditions, and others not (see 0 for details; Csukly et al., 2011; de la Asuncion et al., 2015; Destoop et al., 2012; Gradin et al., 2014; McClure et al., 2007; Radke et al., 2013; Scheele et al., 2013; Wang et al., 2014). There are a number of challenges in social decision-making research in psychiatric illness. Currently there is not a clear characterisation of the precise nature and neural mechanisms of the deficits. Clarifying these will not only provide target processes for treatment, but also show the target brain systems. By developing an understanding of the psychopharmacology of social decision-making in healthy populations, these challenges can be addressed. This would reveal the normal brain systems and candidate modulatory systems involved in these processes.

Social decision-making is an important domain because it moves beyond more traditional methods of social cognition research, and attempts to study the integration of a number of social processes in ecologically valid interpersonal interactions. As a field it utilises tasks with their origins in behavioural

economics, and adaptations of these tasks. Two such examples are the Ultimatum Game (UG) and Prisoner's Dilemma (PD). They have been introduced in detail elsewhere in this thesis. Between them they model trust, cooperation, social expectations and responses to violations of social norms.

Unfair offers in the UG have been shown to consistently activate a network of brain regions, including the anterior insula, anterior mid-cingulate gyrus (aMCC) and medial prefrontal cortex (mPFC), putamen and supplementary motor area (Gabay et al., 2014). Interpretations for these activations are covered in detail in 0, but will be repeated here in brief. Sanfey et al (2003) provided evidence that the strength of anterior insula activation predicted rejection rates in the UG. They concluded that this represented the negative emotion of being treated unfairly, and that this negative emotion drove rejection behaviour. The finding that insula activation was present in the absence of a strong emotional response when responding to unfair offers on behalf of a third party, however, suggests that anterior insula signals inequality and social norm violation, regardless of whether the person is directly involved in the outcome of the game (Civai et al., 2010a; C. Corradi-Dell'Acqua et al., 2013). Conversely, aMCC/mPFC activation has been found to be specific to decisions regarding unfair offers to the self (Civai et al., 2013, 2015).

There is a less diverse collection of published research investigating the neural correlates of the Prisoner's Dilemma. As outlined in 0 (Section 1.5.2.2), neuroimaging research has reported the involvement of the reward system and classic social cognition areas during the PD (e.g. Gradin et al., 2016; Rilling et al., 2002, 2008, 2004; Suzuki et al., 2011). Specifically, the orbitofrontal cortex

and ventral striatum are interpreted as representing reward during feedback of mutual cooperation, and activation of the superior temporal sulcus (STS), temporal-parietal junction (TPJ) and posterior cingulate gyrus are believed to represent processing of the intentionality of the other player (James K Rilling et al., 2004, 2004; Suzuki et al., 2011).

Previous psychopharmacology research has suggested a role for the serotonin (5-HT) system in social decision-making. Evidence suggests that acute tryptophan depletion (ATD), which reduces the amount of systemic serotonin, alters behaviour in both the UG and PD. In the PD, ATD reduces cooperative behaviour, while in the UG it increases rejection of moderately (30% of the total stake) unfair offers, while not changing rejection rates of lower offers (Crockett et al., 2008; M. J. Crockett et al., 2013; Wood et al., 2006). In terms of 'prosocial' behaviour, these results appear contradictory. Rejection of unfair offers in the UG is considered prosocial because it is thought to be altruistic punishment – punishment of another at a personal cost, but with a benefit to wider society. Cooperative behaviour is also considered prosocial. Therefore, an increase in one is at odds with a reduction in the other when framed through the lens of prosocial behaviour. Unfortunately the lack of psychopharmacological PD studies means these results have not been corroborated by others. In the UG however, *increasing* serotonin availability with acute administration of a selective serotonin reuptake inhibitor (SSRI) has shown the opposite effect of ATD – a *reduction* in rejections of 30% offers (Crockett et al., 2010). The authors of this study interpreted this as being the result of increased harm aversion, with rejection in the context of the UG

bringing harm on one's partner by reducing their payoff. The lack of effect for 10-20% offers in these UG studies could mean that the serotonergic manipulations were not potent enough to effect UG behaviour at the extreme end of norm violations, or that multiple psychopharmacological mechanisms underlie UG behaviour.

In the current study, we aimed to clarify the role of 5-HT in social decision-making by using the potent serotonergic compound 3,4-methylenedioxy-methamphetamine (MDMA). We also aimed to extend our understanding of the processes underling any 5-HT effect by concurrently collecting functional neuroimaging data. As detailed in 0, MDMA increases synaptic availability of 5-HT by reversing membrane transporter proteins, as well as acting as a direct agonist at the 5-HT2A receptor (de la Torre et al., 2004; Green et al., 2003).

MDMA has been shown to alter other social cognitive processes. A number of studies have found that MDMA increases affective, but not cognitive, empathy (Hysek et al., 2013; Kuypers et al., 2014; Schmid et al., 2014). As outlined in 0 (Section 1.2), cognitive empathy is the ability to identify and understand the emotional content the other's experience, while affective empathy involves not only an understanding of how someone else feels, but to some extend *experiencing* those same emotions. Previous research has also found that MDMA reduces recognition of fearful, angry and sad facial expressions (Hysek et al., 2013; Matthew G Kirkpatrick et al., 2014; Schmid et al., 2014). In addition to investigating social decision-making, the current study seeks to reproduce these findings of MDMA on empathy and facial affect recognition.

We had participants complete adapted versions of the UG and PD. Full details of the version of these tasks can be found below, in Section 4.3. Participants played multiple single-shot UG rounds with players who offered amounts ranging from 10% to 90% of the total stake. We hypothesised that MDMA would reduce rejection rates of low offers (10-20%) when they were directly affected by the outcome of the game (first person condition, FP). We also had participants make decisions on behalf of a third-party (TP), where their own outcome was not affected by their decision. We hypothesised that in these cases, MDMA would not reduce rejection rates. Activity in brain regions identified in the meta-analysis reported in 0 (Gabay et al., 2014) was hypothesised to be altered in the placebo session, and that MDMA would affect these changes in activity. Specifically, we expected MDMA to reduce the mPFC response to unfair offers in the FP condition, while having no effect on AI activation.

In the PD, participants played with both trustworthy (mostly cooperative) and untrustworthy (mostly competitive) players, as well as an explicit computer opponent (game server; non-social control). We hypothesised that MDMA would increase cooperation with both types of 'human' opponent, as well as increase self-reported trust in each opponent. We expected that none of these changes would be seen when playing the game server. We hypothesised that regions involved in social cognition, including the STS, TPJ and the posterior cingulate cortex would show increased activity when playing the game in the MDMA session compared to the placebo session.

We expected to reproduce previous findings on the effect of MDMA on facial affect recognition and empathy. Specifically, we expected MDMA to reduce recognition of negative facial emotions (anger, fear), and increase affective but not cognitive empathy in the MET.

Before reporting the study investigating the effects of MDMA on social cognition, I will report the validation study investigating the version of the PD and UG used.

4.3 Validation of the Ultimatum Game and Prisoner's Dilemma

4.3.1 Abstract

The Ultimatum Game (UG) and Prisoner's Dilemma (PD) are frequently-studied tasks investigating interpersonal interactions. With evidence accumulating that there are behavioural differences between healthy samples and those with psychiatric disorders, psychopharmacological studies are needed to aid understanding of how the processes underlying these tasks are implemented in the healthy brain. Such approaches require that performance stability is known. We have carried out a test-retest reliability study to aid design and interpretation of future modulatory studies of the UG and PD. 15 (6F) participants completed the UG at least one week apart. To assess reliability across sessions, variance components were extracted from a generalized linear mixed effects model, with each participant entered as a random effect. This enabled comparison of within- and between-participant variance. Performance in the tasks themselves was also assessed, using the generalized estimating equations method. The UG showed acceptable between-session reliability (Rs ranging between 0.52 an and 0.82). Trust ratings of the other players in the PD were reliable between sessions (Rs ranging between 0.76 and 0.92). There was poor reliability across sessions of the PD, with regard to the number of compete decisions (Rs ranging from 0.18 and 0.48). However, there was a failure for the method to converge on the covariance matrix, making these results difficult to interpret. These results are discussed in the context of using these tasks in repeated-measures study designs.

4.3.2 Introduction

Psychopharmacological research often utilises repeated-measures designs, with participants carrying out the same tasks in a number of experimental sessions. When designing these studies, it is important to consider the test-retest reliability of the tasks being used. Test-retest reliability is a measure of the variance in participants' responses to a task across multiple time points, in the absence of an experimental manipulation. Tasks with high reliability will have greater power to detect an effect of a manipulation than those with poor test-retest reliability.

The current study was designed to assess the test-retest reliability of a version of the Ultimatum Game (UG) and Prisoner's Dilemma (PD). These were the versions proposed for use in the MDMA study reported later in this chapter. It should be noted that while the PD remained unchanged, the UG was further altered from the version reported here. These alterations followed a discussion with Dr Molly Crockett, who has published a number of UG studies, and occurred after the validation study had been conducted. Full details of these changes are given in Section 4.4.3.2 below, which outlines the methodology of the MDMA study. The results of the validation study presented here remain informative, as the changes were relatively minor and did not affect the overall task methodology. Here, I provide details of the UG version used in the test-retest study.

In order to convince study participants that they are interacting with real people in social decision-making tasks, different cover-stories are created about where other players' responses originate. In the version of the games presented here,

participants were led to believe that they were logged onto an online network set up as part of a collaboration between King's College London, University College London and Imperial College London. They were told that the people they were to interact with were also logged on to the network at one of these three sites. They were told that these participants may or may not be taking part in an MRI or drug study, but regardless of the exact study they are involved in, the researchers were interested in the same social processes as the current project. They were also told that all participants would be financially reimbursed based on their responses in the UG. There was no such reimbursement based on the decisions made in the PD, which was played on a points-based system. The aim of this cover story was to enhance the feeling of socially interacting with other people when making decisions in the tasks.

The aim of this study was to assess the test-retest reliability of these tasks, and to evaluate their outcomes for comparison to those in the literature. To this end, we had participants complete both tasks, one week apart, and tested their results for reliability. We took the outcome measures from their first session to assess the results of the task and compare them to those found in the literature.

4.3.3 Methods

4.3.3.1 Participants

Fifteen participants (7 female) were recruited by advertising through King's College London's research volunteer portal. While the drug study reported in this chapter (Section 4.4 below) only included male participants, both genders

were included in this validation to make the results more generalizable. Participants played a repeated, single-shot UG and repeated, iterated PD on two separate occasions at least one week apart (mean: 8.5 days; range: 7 – 16 days). Written informed consent was obtained from each participant, and ethical approval granted by the King's College London's Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM 14/15-10).

4.3.3.2 Procedure

Due to the length of these tasks, each was split in two to mitigate against task fatigue. Participants first completed one run of the UG (11 minutes 45 seconds), followed by one run of the PD (9 minutes 15 seconds). This was then repeated.

Ultimatum Game

This version of the UG has three conditions: first-party (FP), third-party (TP) and a non-social control condition, the game server condition (GS).

In the FP condition, participants make a decision to reject or accept an offer made directly to them. The premise of this condition is that both they and the proposer will be affected monetarily by their response. In the TP condition, participants are shown an offer from one person to another, and are asked to make a decision on behalf of the other player. In this condition the rules of the game are the same, but the participant themselves are not directly affected by the outcome. For example, if they see 'John' offering 'Simon' £4 out of £20 and the participant chooses to accept this offer, 'Simon' receives £4 and 'John' keeps the remaining £16. If the participant rejects this offer, neither 'John' nor 'Simon' receives any money for that round. In neither outcome does the

participant receive or lose any money. In the GS condition, the participant is told that the offer they receive is a random, computer-generated offer. In this condition, their decision solely affects their own payoff.

While the majority of published studies investigate offers from 10-50% of the total stake, the present study includes “hyper-fair” offers of 80% and 90%. All offers were out of a total stake of £20. The number of each offer level is given in Table 4-1. These offer levels were presented in each in condition, leading to a total of 144 offers, split equally across runs on each session. Figure 4-1 shows the order of presentation and timing of each round of the task. Participants were also asked to make five offers, acting as the proposer, in each run of the game. They were able to make offers in increments of 10% of the total stake. Participants were told that they would be paid one percent of the total amount they earn during the course of the study; in reality participants were paid a fixed sum of £20.

Table 4-1: Number of each offer level and the fairness level assigned for the sake of analysis

Offer level (%)	Number of offers at this level	Fairness level
10	8	Unfair
20	8	
30	4	N/A
40	4	

50	8	Fair
80	8	Hyper-fair
90	8	

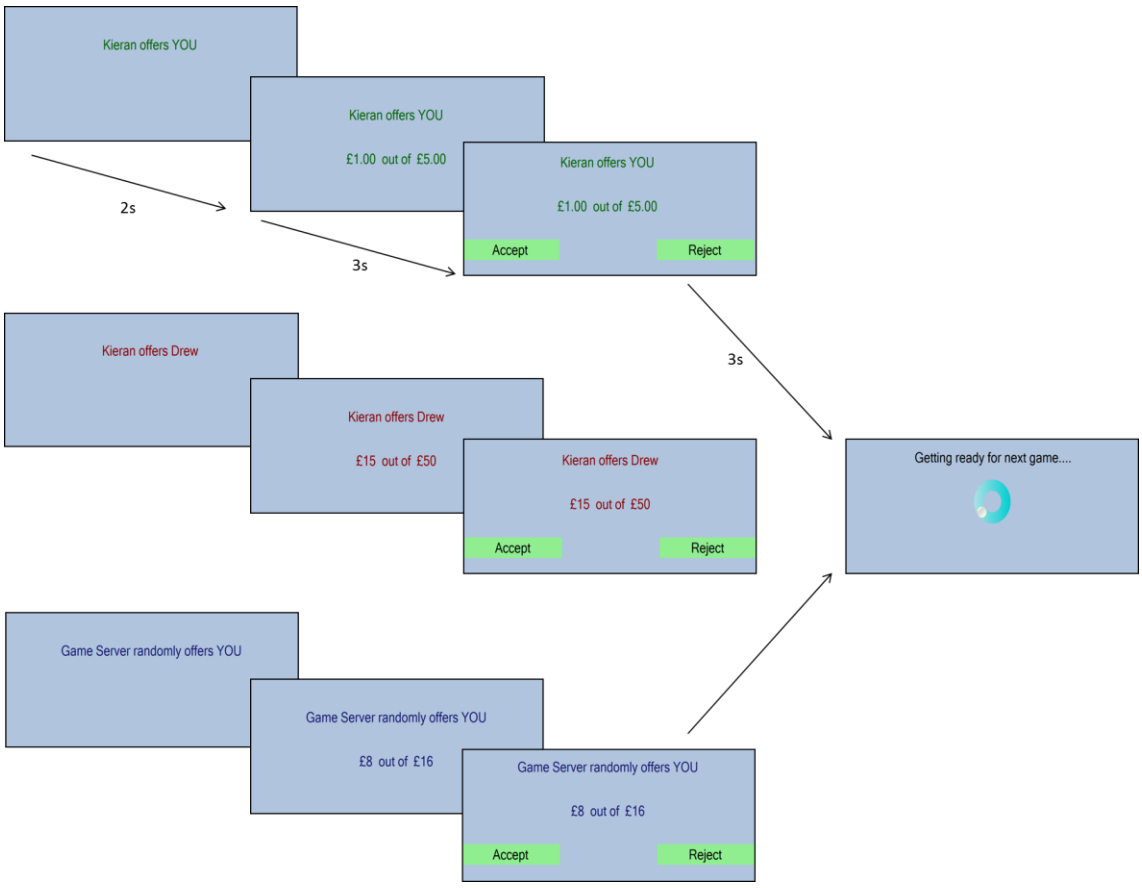


Figure 4-1: Diagram depicting the three conditions of the UG task. Green writing: first person condition; red writing: third-party condition; blue writing: game server condition

Prisoner's Dilemma

As mentioned above, the PD was split into two runs. In each run, participants played with three other 'players', and were told that the middle player was in fact a random response generator, which did not learn from the participant's responses. This condition was included as a non-social control condition and was referred to as the Game Server (GS).

See Figure 4-2 for details of the PD game. In this version of the PD, the participant played multiple rounds with each player. They were told this could be

any number of rounds between eight and fifteen but it was in fact set at fifteen rounds per player. The number of rounds was undisclosed as evidence suggests disclosure can affect behaviour in the game (Ghoneim et al., 2007; Normann and Wallace, 2012).

On each round, players first made a Compete or Cooperate decision simultaneously with the other player. They were then given feedback as to what the other player did and how the points are distributed. They were then asked to rate their trust in the other player.

While the participants believed that the other 'players' were real people logged onto a network, they were in fact pre-programmed with set responses. One player in each run was programmed to be trustworthy, making mostly Cooperate decisions (12 out of 15 decisions to cooperate), while the other was untrustworthy (12 out of 15 decisions to compete). In the first run of each session the order of opponents was: Trustworthy – GS – Untrustworthy. In the second run of each session the order of opponents was: Untrustworthy – GS – Trustworthy.

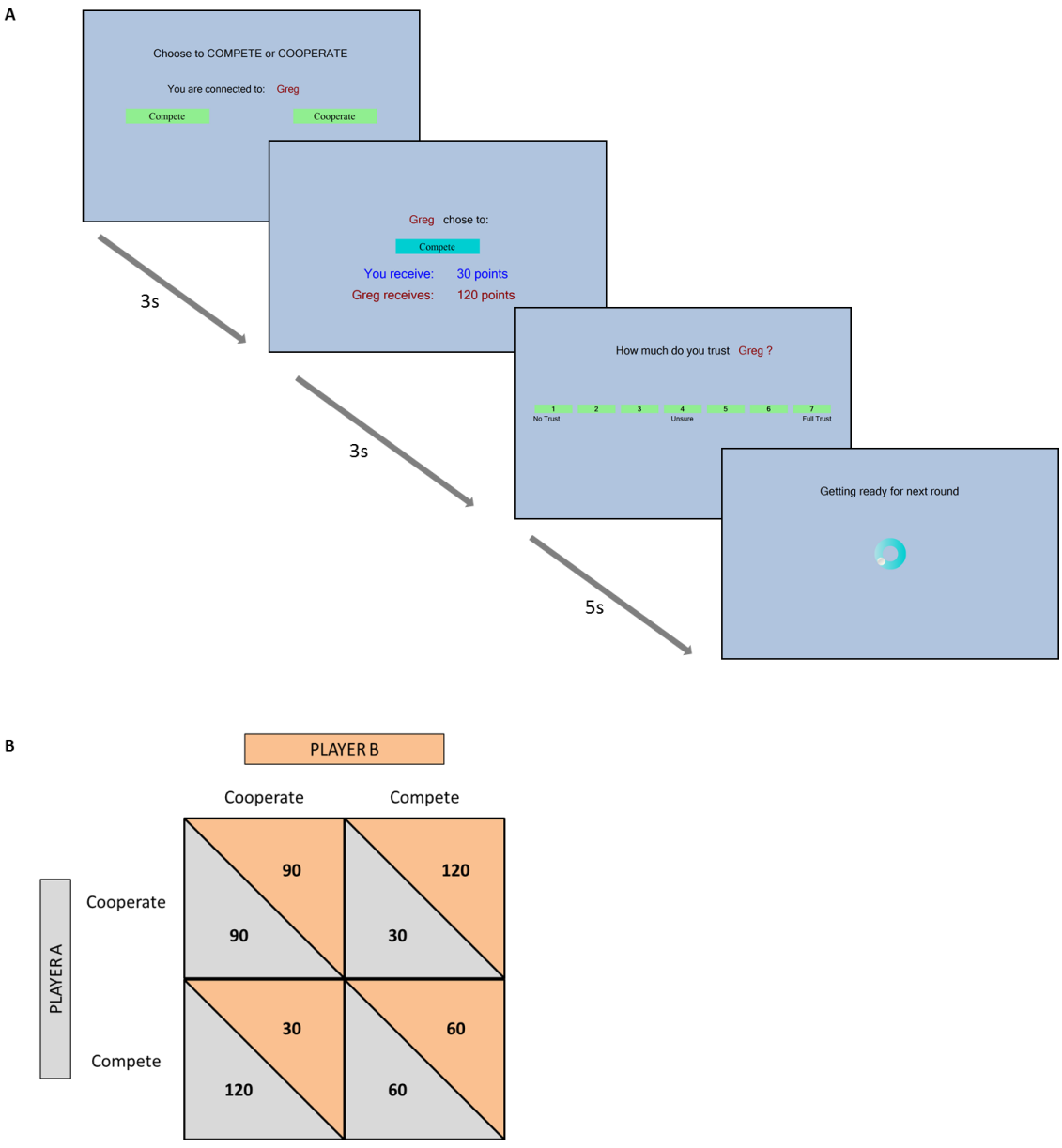


Figure 4-2: The Prisoner's Dilemma. A) Diagram depicting the paradigm with timings; B) payoff matrix

4.3.3.3 Data analysis

The raw responder data for the UG comes in the form of dichotomous accept/reject decisions for each offer. There were 16 offers each from the unfair and hyper-fair levels, and eight fair offers, spread equally over two runs of the

task. Participants were also asked to make offers to other players – here the raw data is an absolute value of a total stake (always £20).

Two forms of data come from the PD. First, trust ratings are given after each round of the game. This is a number from 1 to 7. Second are dichotomous compete/cooperate decisions on each round of the game.

Test-retest reliability – Ultimatum Game: rejection rates

A popular statistic for test-retest reliability is the intraclass correlation coefficient (ICC) (Shrout and Fleiss, 1979). The ICC gives the proportion of the total variance (between- and within-participant) that can be explained by the between-participant variance. As the method uses the variance components of a repeated-measures ANOVA, it is not an appropriate measure for non-Gaussian data such as the binomial or proportion data collected here (Nakagawa and Schielzeth, 2010).

We have used the rptR package (version 0.6.405, Nakagawa and Schielzeth, 2010) implemented in the R statistical environment (R Development Core Team, 2015). We entered each participant as a random effect into a generalised linear mixed model (GLMM) and extracted variance components to obtain an estimate of repeatability on a logit-link scale. An estimate of more than 0.6 was considered an acceptable level of reliability. This represents 60% of the total variance being explained by between-participant variance.

As data was collected in two runs per session, reliability of two types have been analysed – first, the reliability of responses across runs within session one (henceforth, ‘within-session reliability’); second, the reliability of responses

combined across runs of each session, across sessions (henceforth, 'between-session reliability').

Test-retest reliability – Ultimatum Game: proposals

Each offer was converted to a percentage of the total stake, and the mean offer calculated. We calculated an absolute, two-way, mixed model intraclass correlation coefficient (ICC; Shrout and Fleiss, 1979). The ICC gives the proportion of the total variance (between- and within-participant) that can be explained by the between-participant variance. An ICC greater than or equal to 0.6 was considered acceptable.

Outcome of session one – Ultimatum Game

The data collected was in the form of categorical (accept or reject) responses to monetary offers. Converting this data to proportions and analysing with an ANOVA is problematic on two fronts. First, the proportion data is non-normally distributed. Second, the variance of binomial distributions does not show homogeneity, thus violating the assumptions of ANOVA (Jaeger, 2008).

As such, the current data have been analysed using repeated-measures logistic regression, implemented with generalized estimating equations using IBM SPSS Statistics for Windows (IBM Corp., 2012). This is a nonparametric test which takes into account the correlation of responses within subjects, and produces a chi-squared statistic (χ^2), an odds ratio (OR) and its 95% confidence interval (CI), and a *p*-value. It is a recommended approach to analysing categorical data that has been used in a number of studies in the UG literature (M. J. Crockett et al., 2013; Hanley et al., 2003; Koenigs et al., 2007; Koenigs

and Tranel, 2007). The odds ratio represents the change in probability of an event (in this case, a rejection) occurring with a change in condition (fairness, offer origin etc.).

Test-retest reliability – Prisoner's Dilemma: Trust ratings

For each category of opponent (Trustworthy, Untrustworthy, non-social control (GS)), the final eight trust ratings were averaged, giving a rating per opponent. We calculated an absolute, two-way, mixed model intraclass correlation coefficient (ICC; Shrout and Fleiss, 1979). The ICC gives the proportion of the total variance (between- and within-participant) that can be explained by the between-participant variance. An ICC greater than or equal to 0.6 was considered acceptable.

Test-retest reliability – Prisoner's Dilemma: Compete decisions

The dichotomous compete/cooperate decisions were repeated 15 times with each opponent. As with the UG data, we have used the rptR package (version 0.6.405, Nakagawa and Schielzeth, 2010) implemented in the R statistical environment (R Development Core Team, 2015). We entered each participant as a random effect into a generalised linear mixed model (GLMM) and extracted variance components to obtain an estimate of repeatability on a logit-link scale. An estimate of more than 0.6 was considered an acceptable level of reliability. This represents 60% of the total variance being explained by between-participant variance.

Again, as with the UG, as data was collected in two runs per session, reliability of two types have been analysed – first, the reliability of responses across runs

within session one (henceforth, ‘within-session reliability’); second, the reliability of responses combined across runs of each session, across sessions (henceforth, ‘between-session reliability’). This is true for both the trust ratings and decision data.

Outcome of session one – Prisoner’s Dilemma

The trust rating outcomes were averaged across both runs of each category of opponent (Trustworthy, Untrustworthy, GS). These were then entered into a one-way ANOVA, with post hoc pairwise comparisons.

As with the UG, the dichotomous decisions were analysed using repeated-measures logistic regression, implemented with generalized estimating equations using IBM SPSS Statistics for Windows (IBM Corp., 2012). This method has been used in a number of studies investigating the PD (Duffy and Smith, 2014; Reed et al., 2012; Sparks et al., 2016), and is a recommended approach for repeated-measures dichotomous outcomes (Hanley et al., 2003).

4.3.4 Results

4.3.4.1 Ultimatum Game

Test-retest reliability – within-session

This section presents the reliability of responses between runs in the same session. Table 4-2 shows the Repeatability (R) estimates and their 95% confidence interval (CI) for the rejection rates of each fairness level in each

condition. Figure 4-3 displays the change in rejection rate of each participant across runs within session one. Generalized mixed models attempt to estimate a covariance matrix of repeated measurements. When there is little variation in response, this is not possible, resulting in a failure to 'converge' on a covariance matrix. In the current data there was not enough variability in responses to Fair and Hyper-fair offers in the FP and GS conditions to calculate a repeatability statistic, meaning that these conditions showed very high reliability.

Responses to Unfair offers in all three conditions were highly reliable (FP: R = 0.96, CIs: 0.96 – 0.99; TP: R = 0.96, CIs: 0.93 – 0.99; GS: R = 0.84, CIs: 0.59 – 0.98), as were responses to Fair offers in the TP condition (R = 0.84, 95% CIs: 0.59 – 0.98). Response to TP Hyper-fair offers showed poor test-retest reliability (R = 0.32, CIs: 0 – 0.86).

The proposer data showed a high level of test-retest reliability across runs within-session (ICC = 0.85, CIs: 0.54 – 0.95).

Table 4-2: Repeatability (R) estimates of UG responses across runs within session one, with 95% CIs in brackets for each condition across fairness levels. NV = Not enough variation: almost all participants accepted all offers in both sessions

	Fairness Level		
Condition	**Unfair**	**Fair**	**Hyper-fair**
FP	0.96 (0.96 – 0.99)	N/V	N/V
TP	0.96 (0.93 – 0.99)	0.84 (0.59 – 0.98)	0.32 (0 – 0.86)
GS	0.84 (0.59 – 0.98)	N/V	N/V

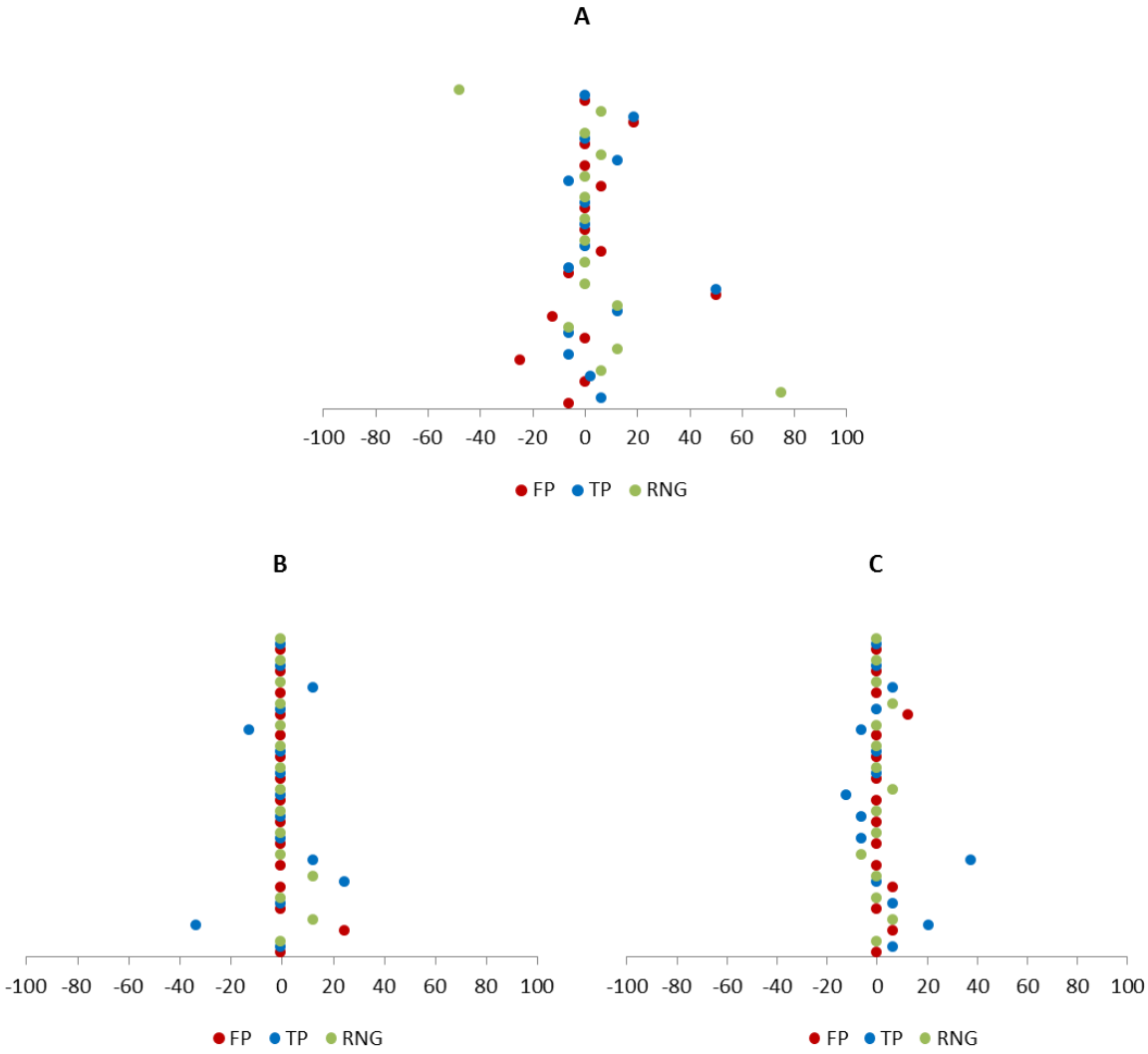


Figure 4-3: Within-session change in rejection rate for each participant in each condition across fairness levels. A) Unfair; B) Fair; C) Hyper-fair

Test-retest reliability – between-session

This section presents the between-session reliability of UG responses in each condition and at each fairness level. Figure 4-4 displays the change in rejection rate of each participant between sessions. The FP Hyper-fair and GS Fair conditions did not show enough variation to produce a repeatability statistic, meaning that these conditions showed very high reliability.

All Unfair and Fair offers across all conditions showed good reliability between sessions (range of *R*: 0.76 – 0.82). Hyper-fair offers in the TP and GS had a repeatability statistic, *R* = 0.57; this is lower than the cut-off of 0.6 which we had defined as being a good repeatability.

The proposer data showed very high reliability between sessions (ICC = 0.92, CIs: 0.75 – 0.97).

Table 4-3: Repeatability (R) estimates between sessions, with 95% CIs. N/V = Not enough variation

	Fairness Level		
Condition	**Unfair**	**Fair**	**Hyper-fair**
FP	0.79 (0.48 – 0.97)	0.82 (0.53 – 0.95)	N/V
TP	0.76 (0.41 – 0.93)	0.82 (0.53 – 0.95)	0.57 (0.06 – 0.87)
GS	0.82 (0.53 – 0.78)	N/V	0.57 (0.02 – 0.84)

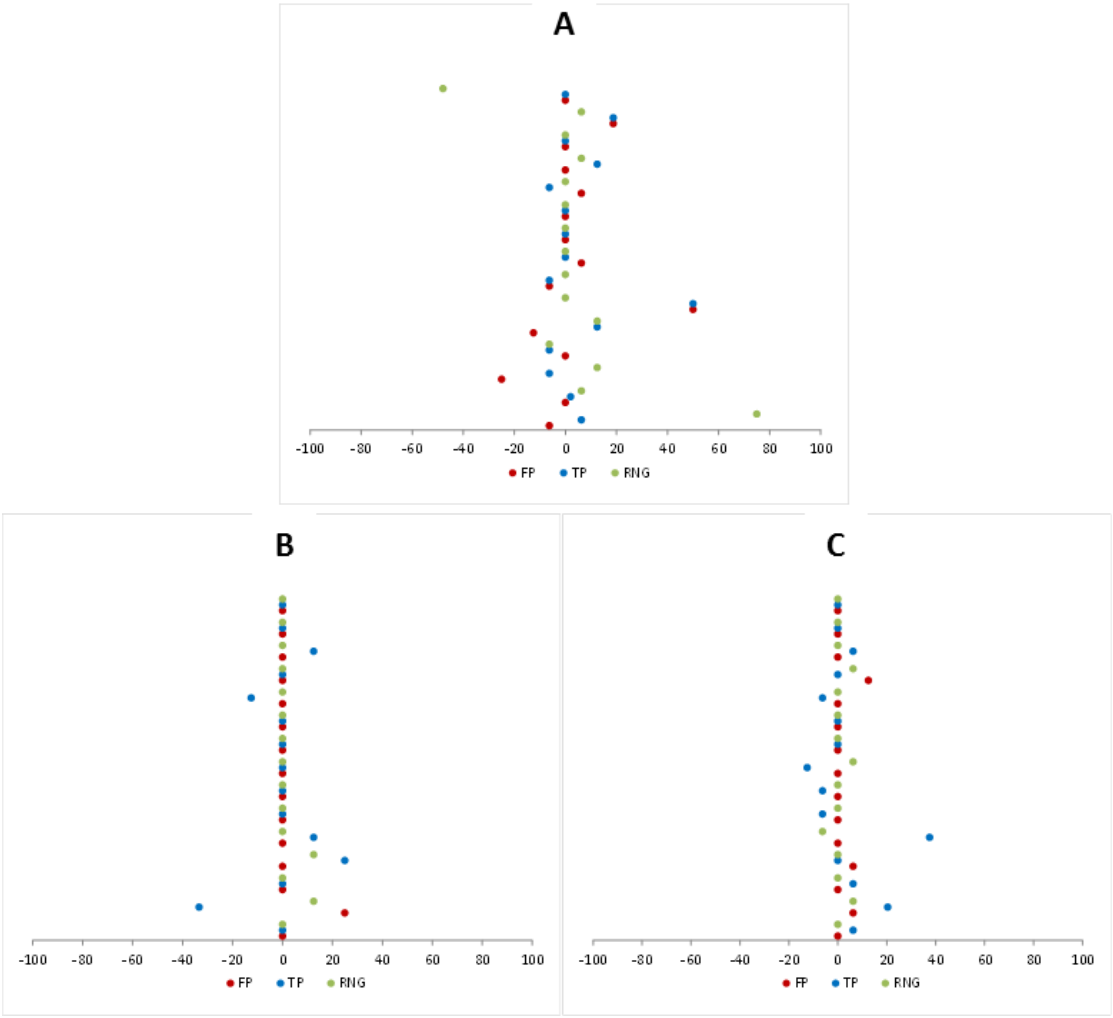
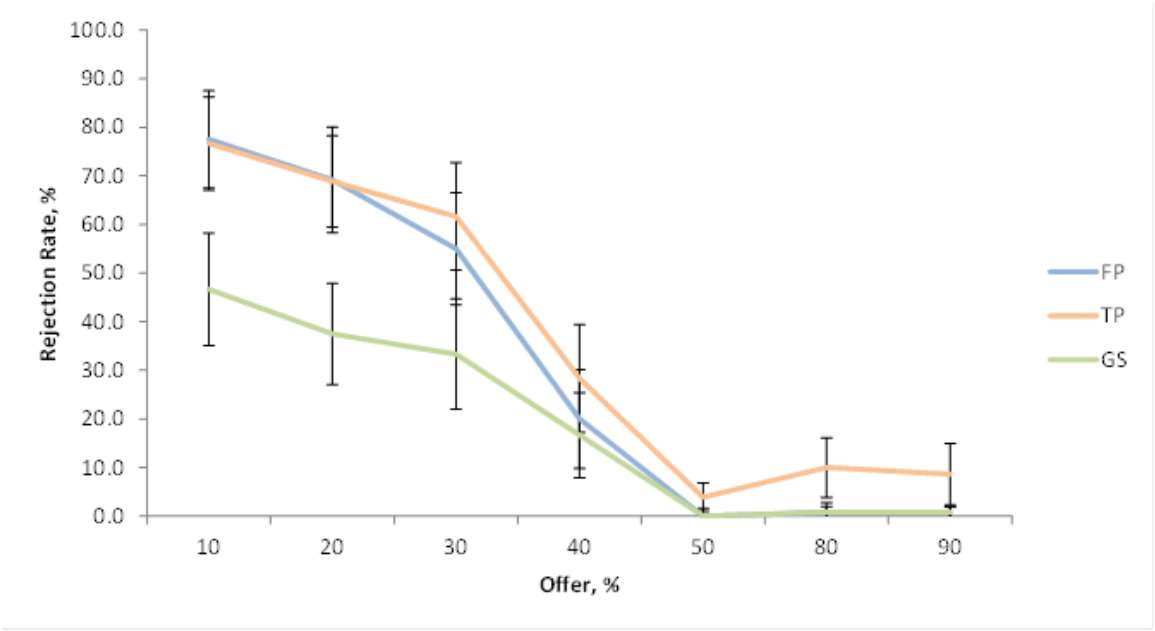


Figure 4-4: Between-session change in rejection rate for each participant in each condition across fairness level. A) Unfair; B) Fair; C) Hyper-fair

Outcome of session one

Figure 4-5A displays the rejection rates of each offer level in session one, combined across runs. In line with the published literature, rejections rates decreased with increasing offer level (Civai et al., 2013; M. J. Crockett et al., 2013; Gabay et al., 2014; Güth et al., 1982; Sanfey, 2003) in all conditions. Figure 4-5B displays the rejection rates when these are grouped into Unfair, Fair, and Hyper-fair offers.



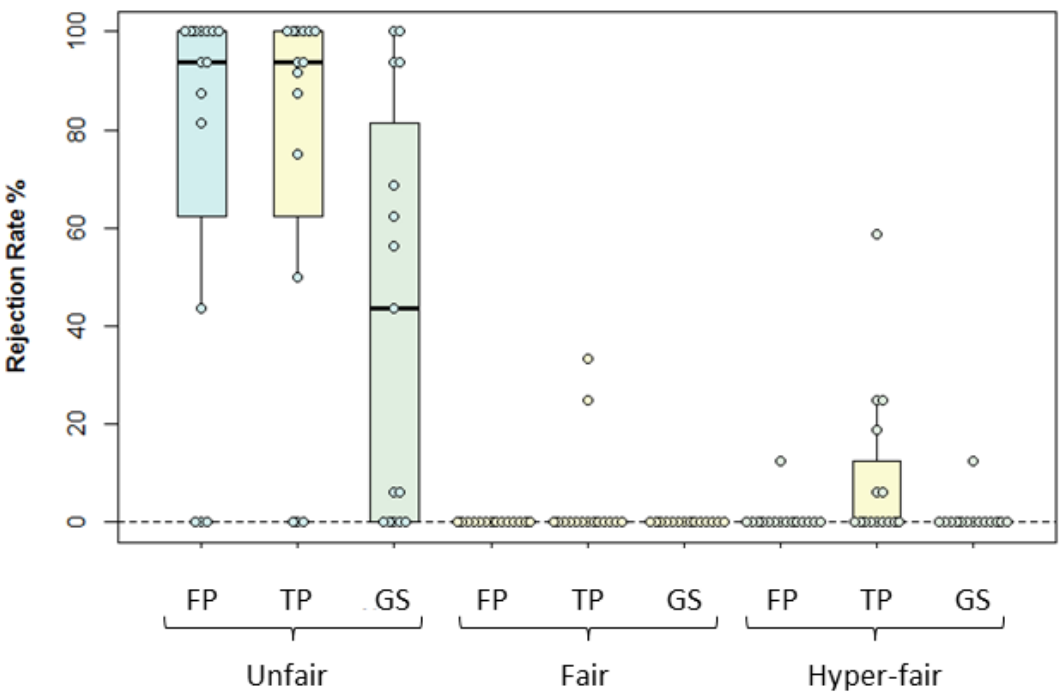


Figure 4-5: Rejection rates combined across runs in session one. A) Rejection rate per offer; B) Rejection rates when grouped into Unfair (10-20%), Fair (50%) and Hyper-fair (80-90%) offers. Error bars: +/- 1 SE. FP: First-person condition; TP: third-person condition; GS: game server

There was a statistically significant reduction in the probability of rejecting an offer in the non-social control condition (GS) compared to both the FP and TP conditions (FP vs GS: $\chi^2_{(1,14)} = 9.77$, OR = 0.3, $p = 0.002$; TP vs GS: $\chi^2_{(1,14)} = 13.26$, OR = 0.227, $p < 0.001$), but no change between the FP and TP conditions ($\chi^2_{(1,14)} = 2.59$, OR = 1.49, $p = 0.11$).

There was statistically significant reduction in the probability of rejecting an offer in both the Fair and Hyper-fair conditions compared to the Unfair condition (Unfair vs Fair: $\chi^2_{(1,14)} = 47.71$, OR = 0.01, $p < 0.001$; Unfair vs Hyper-fair: $\chi^2_{(1,14)} = 45.22$, OR = 0.02, $p < 0.001$). There was no change in rejection rates between the Fair and Hyper-fair conditions ($\chi^2_{(1,14)} = 2.32$, OR = 0.392, $p = 0.127$). Furthermore, gender was included in the model, and there was no main effect, nor any interaction between gender and fairness or offer origin (all *p*s > 0.303).

Figure 4-6 displays a histogram of mean offer in session one. There was a statistically significant difference of mean offer from the lowest possible offer of 10% (mean: 47.3, SD = 13.2; one-sample $t_{(14)} = 10.97$, $p < 0.001$).

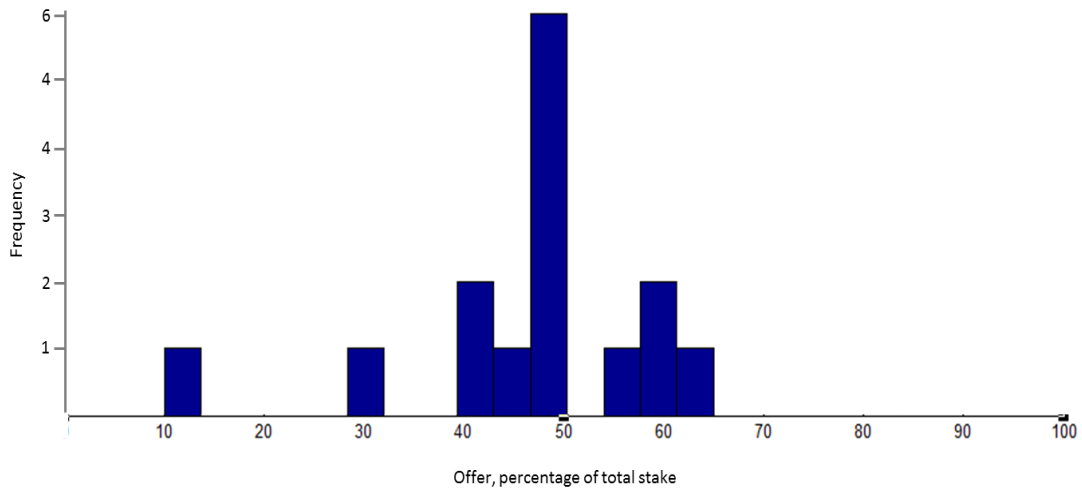


Figure 4-6: Histogram of mean offer in session one

4.3.4.2 Prisoner's Dilemma

Test-retest reliability – trust rating

Table 4-4 shows the ICC for the Trust ratings with each category of opponent. There was good reliability for all conditions, both within- and between sessions (ICC range: 0.75 – 0.96). The change for each participant is shown in Figure 4-7.

Table 4-4: ICC for the Trust ratings for each category of opponent, both within- and between-sessions

Opponent	Within-session	Between-sessions
Trustworthy	0.75	0.92
Untrustworthy	0.86	0.76
GS	0.89	0.96

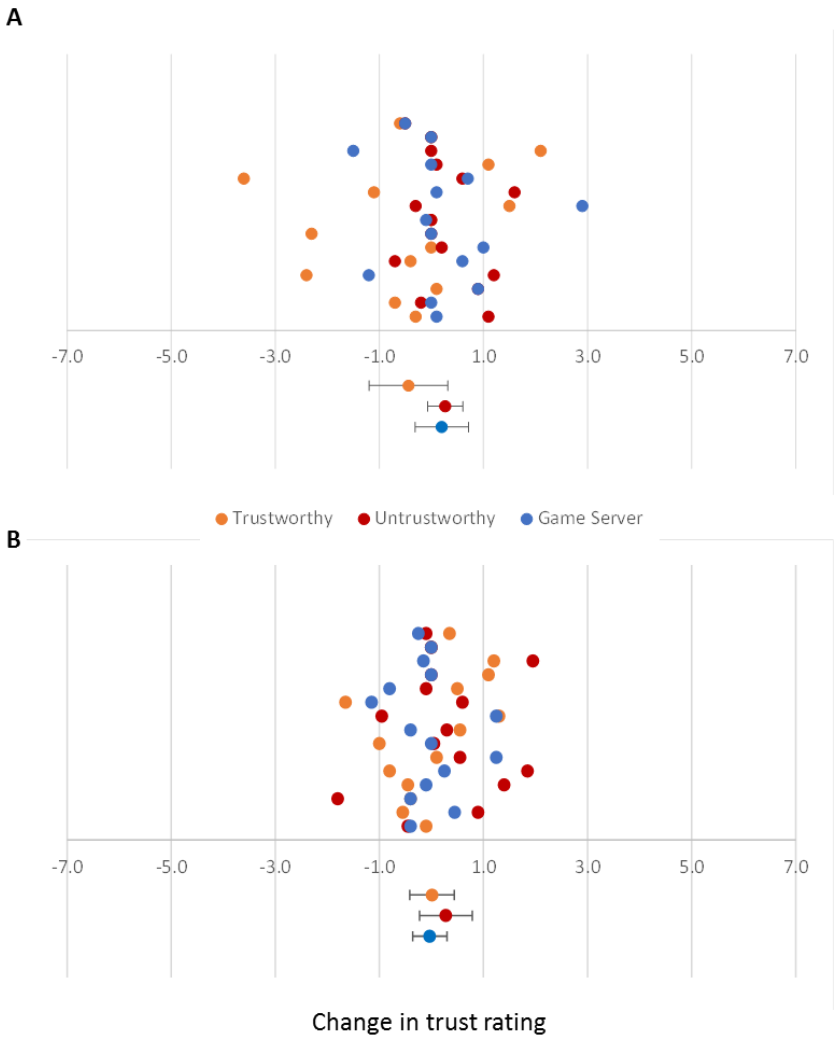


Figure 4-7: Change in trust ratings for each category of opponent. A) Within-session changes; B) Between-session changes. Points below the *x*-axis are the mean for that category with 95% CIs

Test-retest reliability –Compete decisions

As stated in Section 4.3.3.3, a generalized linear mixed model (GLMM) approach was used to estimate the between- and within-participant variance components of the proportion data. GLMMs estimate the maximum likelihood of the of model parameters. It is not always possible to estimate the maximum likelihood for a number of reasons, including overly complex models, small sample sizes, small estimated variances or large uncertainties (Bolker et al., 2009; Williamson et al., 2013). This can result in 'convergence errors'. If such an error occurs one cannot be certain the output of the test is reliable.

Such convergence errors occurred when calculating the repeatability in the current dataset. Nonetheless, the repeatability estimates are displayed in Table 4-5 for the change in percentage of Compete decisions for each category of opponent. None of the repeatability estimates were above 0.6 (range 0.18 – 0.48), suggesting that the test-retest reliability for this outcome measure is not good. However, as stated above, it is unknown how reliable these estimates are. The change for each individual is displayed in Figure 4-8, with the median and interquartile range displayed below the *x*-axis.

The median change in response for all categories when considering both within- and between-session analyses were very close to zero, with the largest interquartile range being ±11% (Trustworthy opponent, within-session).

Table 4-5: Repeatability estimates of the proportion of Compete decisions, both within- and between-sessions. Note that the GLMM failed to converge, rendering these estimates unreliable.

Opponent	Within-session	Between-sessions
Trustworthy	0.18 (0 – 0.35)	0.27 (0.1 – 0.47)
Untrustworthy	0.34 (0.13 – 0.52)	0.26 (0.09 – 0.40)
GS	0.36 (0.11 – 0.55)	0.48 (0.23 – 0.63)

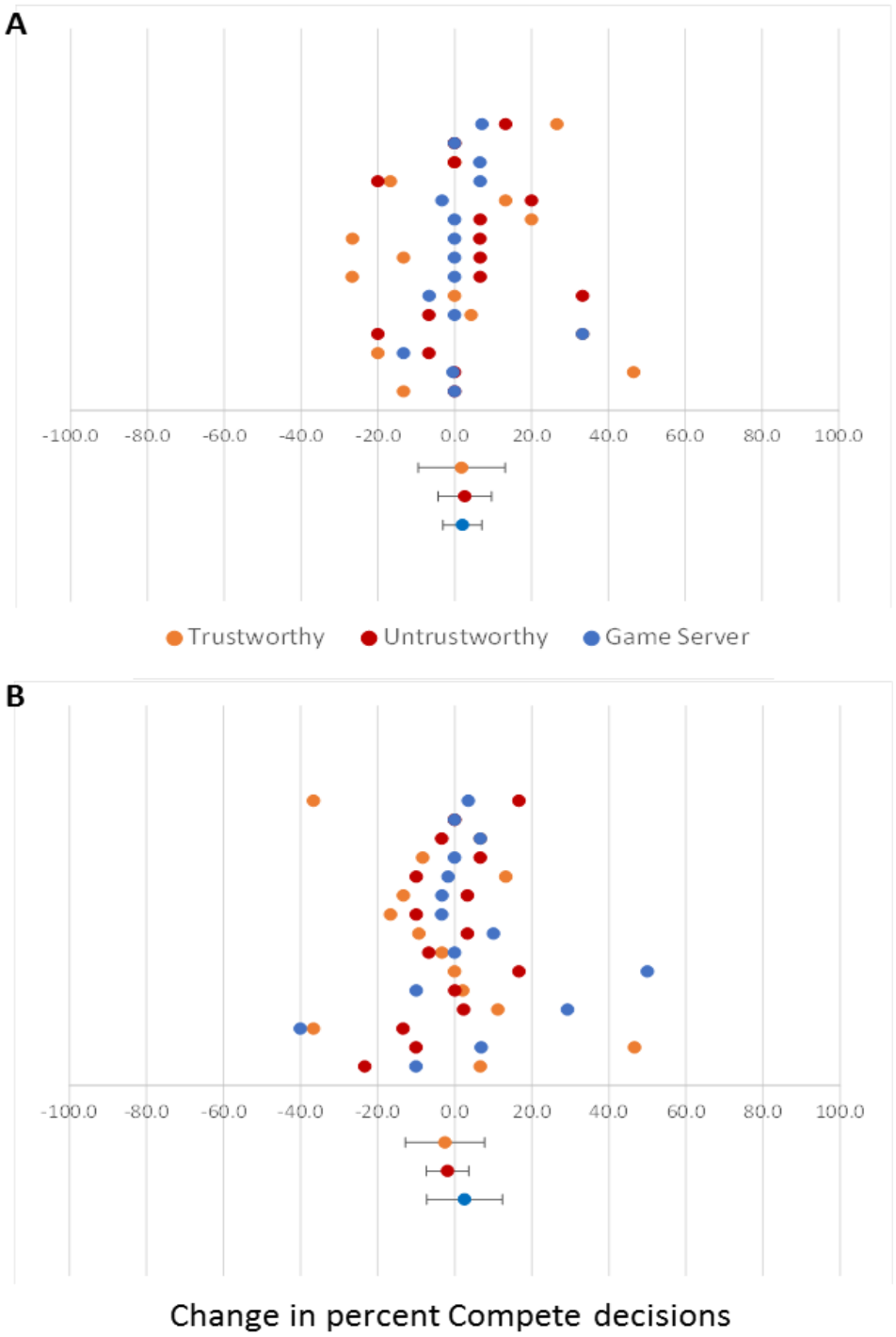


Figure 4-8: Change in the percentage of Compete for each category of opponent. A) Within-session changes; B) Between-session changes. Points below the x-axis are the median for that category, error bars: interquartile range

Outcome of session one – trust ratings

Figure 4-9A displays the mean trust ratings of the final eight rounds for each category of opponent, averaged across runs in session one. A repeated-measures ANOVA reveals a main effect of opponent ($F_{(2,28)} = 20.96$, $p < 0.001$, $ή^2 = 0.6$, Greenhouse-Geisser). Post-hoc pairwise comparisons showed a statistically significant reduction in trust ratings for untrustworthy, compared to trustworthy, opponents (Bonferroni-corrected $p < 0.001$, Cohen's $d = 1.87$) and a statistically significant difference between untrustworthy and game server opponents (Bonferroni-corrected $p = 0.009$, Cohen's $d = 1.12$). The difference between Trustworthy and the non-social control opponent was not statistically different (Bonferroni-corrected $p = 0.085$, Cohen's $d = -0.64$).

Figure 4-9C displays a histogram of the mean trust ratings for the game server. Participants reported different interpretations of what 'trust' meant in this context. In the task, a rating of one was labelled as 'No trust', four was labelled 'Unsure', seven as 'Full trust'. Some participants commented that they had no trust in a computer because one cannot 'trust' a random response generator, while other participants stated that one could neither trust nor not trust the computer, and so they rated it as 'unsure'. These differing interpretations are evident from the binomial shape to the histogram in Figure 4-9C.

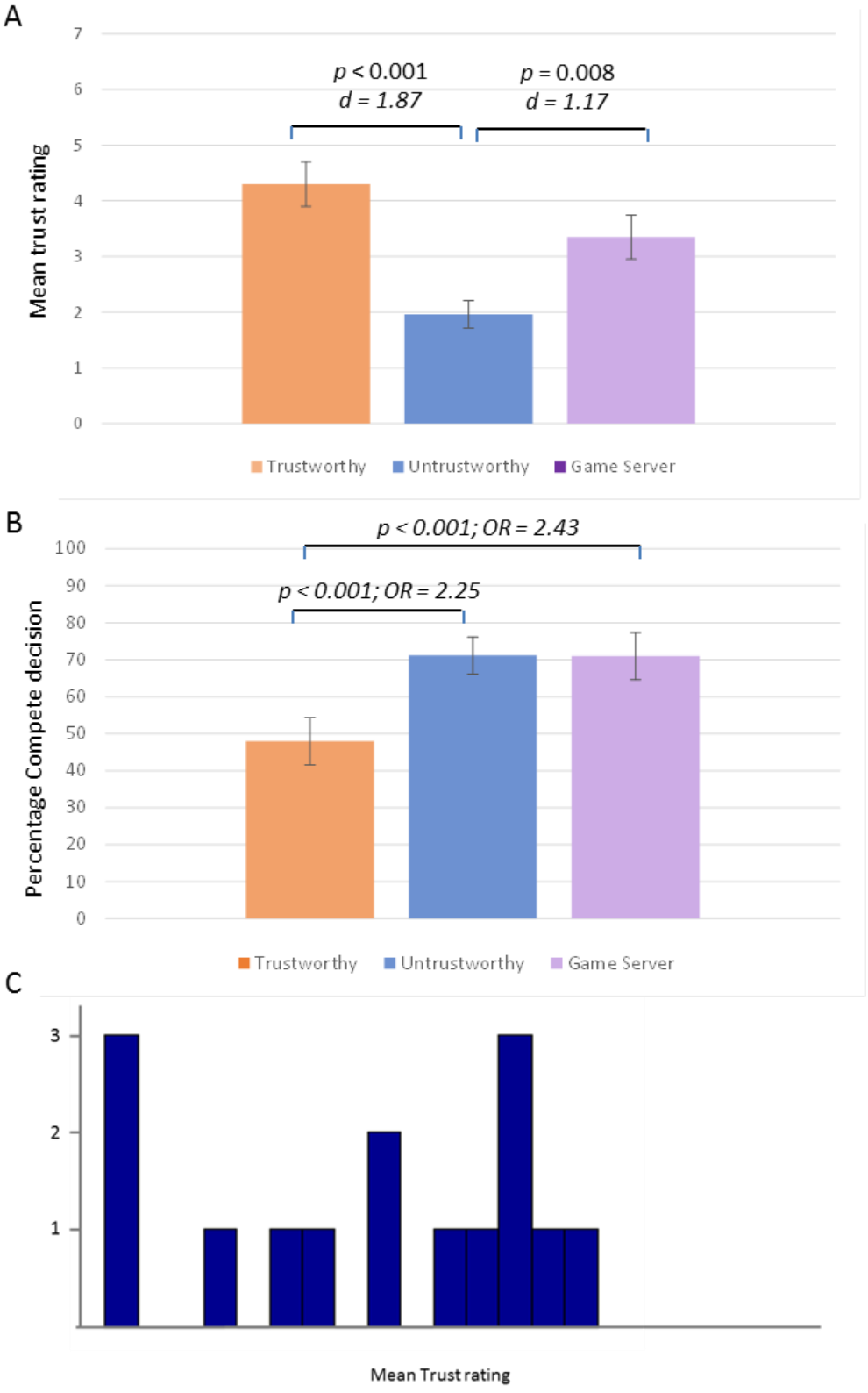


Figure 4-9: PD outcome of session one, averaged across runs. A) average trust rating over the final eight rounds; B) percentage Compete decisions; C) histogram of mean trust ratings for the game server. All *p*-values Bonferroni corrected. Error bars: +/- 1 SE

Outcome of session one – Compete decisions

Figure 4-9B displays the percentage of Compete decisions for each category of opponent. When the opponent was untrustworthy and mostly competed, there was a statistically increased probability of participants making Compete decisions compared to when they were playing trustworthy opponents ($\chi^2_{(1,14)}$ = 15.21, OR = 2.25, $p < 0.001$). Likewise, there was an increase in Compete decisions when playing the non-social control opponent compared to when they were playing trustworthy opponents ($\chi^2_{(1,14)} = 14.47$, OR = 2.43, $p < 0.001$). There was no statistical difference in the proportion of Compete decisions between the non-social control and untrustworthy opponents ($\chi^2_{(1,14)}$ = 0.1, OR = 0.93, $p = 0.754$). Furthermore, when gender was included in the model, and there was no main effect, nor any interaction between gender and trustworthiness ($p = 0.62$ and 0.343, respectively).

4.3.5 Discussion

This study was designed to investigate the test-retest reliability of the versions of the Ultimatum Game (UG)[3] and Prisoner's Dilemma (PD) used in the MDMA study, and to compare the results obtained to those seen in the literature. In this version of the tasks, participants were told that they would play with other

[3] One modification was made to this version of the UG before use in the MDMA study, which is detailed in Section 4.4.3.2

players over an online network developed by researchers as part of a collaboration between King's College London, Imperial College London and University College London. Participants played two runs of each game at each session. Most measures showed good test-retest reliability, with some notable exceptions which will be discussed further below. Task performance aligned with expectations for both tasks. Importantly for the experimental study reported in Section 4.4 (which recruited only male participants), there was no effect of gender in either task.

4.3.5.1 The Ultimatum Game

As with the version of the UG validated in 0, rejection rates decreased with increasing offer in all conditions. There were lower rejection rates in the non-social control condition compared to both the first- and third- party conditions (FP and TP, respectively). These results are in line with UG studies in the literature (Civai et al., 2013; Gabay et al., 2014; Güth et al., 1982; Sanfey, 2003). There was no difference between FP and TP conditions. Studies investigating FP and TP conditions together have also not shown differences between these conditions under 'normal' conditions (Civai et al., 2012a, 2015; C. Corradi-Dell'Acqua et al., 2013). Civai and colleagues did, however, find evidence of a differential effect of transcranial direct current stimulation (tDCS) over the medial prefrontal cortex for FP and TP conditions (Civai et al., 2015). This study found that tDCS reduced rejection rates of unfair offers in the FP, but not TP, condition, suggesting that while behavioural outcomes may be similar under 'normal' conditions, the underlying neural mechanisms may differ.

Examination of the proposer data showed that participants in this study were generally more inclined to offer amounts close to equal, rather than the lowest amount they were able. Although this latter behaviour is that which would be predicted by rational choice and expected utility theory (Glimcher et al., 2009), it is rarely seen in studies of the UG, where people typically offer close to equal offers . As such, proposer data from the current version of the UG is in line with the literature, reviewed and analysed using meta-analysis by Oosterbeek et al (2003).

With the exception of rejection rates of hyper-fair offers in the TP and non-social control conditions, all UG measures showed good test-retest reliability. For those two conditions which did not, the reliability was close to the level which had been specified as acceptable (both conditions R = 0.57; predefined acceptable level: 0.6). Reliability is a measure of the between-participant variance as a proportion of total variance (between- plus within-participant variance). Rejection rates in the hyper-fair conditions were very low for most participants. As such the between-participant variance was also low, and those changes seen within-participant, across sessions, would have had a more prominent effect on the repeatability statistic. Lower-than-ideal reliability means that a larger effect size may be required to find a statistically significant effect of an intervention, as the variance across sessions may be larger than if the reliability were better. With the current task, the hyper-fair conditions are not primary outcome measures, so the reliability of these conditions is not considered problematic.

4.3.5.2 The Prisoner's Dilemma

In this version of the PD, when participants believed they were playing the game with another person (i.e. across trustworthy and untrustworthy conditions), they cooperated approximately 40% of the time. A large meta-analysis of the PD showed that the highest frequency of studies found 30-40% cooperation rates (Sally, 1995; Figure 2 p. 63). It should be noted that this was looking at both iterated and single-shot studies. However, cooperation is repeatedly seen in iterated PD games, despite the game theoretic 'rational' decision being mutual defection (Andreoni and Miller, 1993; Colman, 2003; Cooper et al., 1996).

When broken down into different types of opponents, participants cooperated more (competed less) with cooperative opponents compared to uncooperative opponents (i.e. trustworthy vs untrustworthy). While the same is true when comparing trustworthy opponents to the non-social control opponent, it is interesting that there was no difference in behaviour when playing untrustworthy opponents compared to the non-social control.

The difference in cooperative behaviour between the two social conditions is mirrored by the increased trust ratings for the trustworthy opponent compared to the untrustworthy opponent. It is interesting that this relationship between trust and cooperation wasn't seen when comparing untrustworthy opponents to the non-social control; where there was a difference in trust ratings but not rates of compete decisions. However, there were different interpretations of the idea of 'trust' when referring to the non-social control condition – some participants stated that it was impossible to neither trust nor not trust a random response

generator, while others stated that they had no trust in this condition. Qualitatively, it is possible these could amount to the same thing, and therefore perhaps the percentage of compete decisions are in fact mirrored by the amount of trust in each condition.

The test-retest reliability of participants' trust ratings was high in all conditions. It was not possible to formally assess the reliability of the compete/cooperate decisions, as it was not possible to estimate the maximum likelihood in the GLMM, and therefore not possible to extract the necessary variance components. 'Failure to converge' in GLMM estimations is a recognised problem with the statistical method, with a number of possible reasons underlying it (Bolker et al., 2009; Williamson et al., 2013). Examining plots of the differences in responses across sessions (Figure 4-8) reveals that there is indeed some variation, with a wider relative range than that seen with the trust ratings. However, there was a median change in response very close to zero, and an interquartile range of less than 10% either way. This is comparable to, if not slightly better than, the relative range in TP hyper-fair rejection rates in the UG (which had a repeatability estimate of 0.57). This lower reliability of the task must be taken into account when performing a repeated-measures study with any intervention, as a small effect size may be lost in the within-participant variance.

4.3.5.3 Conclusion

The current study has assessed the validity of the version of the Ultimatum Game (UG) and Prisoner's Dilemma (PD) to be used in a psychopharmacological study with the compound MDMA.

Both tasks produce similar responses to those seen in the literature. While there are some reservations around the retest reliability of the proportion of compete decisions in the PD, the trust rating outcome measure showed good test-retest reliability. Furthermore, the UG, on the whole, also showed good test-retest reliability.

4.4 The effect of MDMA on social cognition

4.4.1 Abstract

With growing interest in the social cognitive deficits of psychiatric conditions, it is vital to investigate the psychopharmacology of these functions in healthy individuals. To this end, we administered 3,4-methylenedioxymethamphetamine (MDMA), a compound known for potent social effects, prior to playing an Ultimatum Game (UG) and Prisoner's Dilemma (PD) during functional neuroimaging. We employed a double-blind, placebo-controlled, crossover design. 100mg of MDMA or a placebo was administered to 20 healthy, male volunteers prior to playing an iterated PD with a 'trustworthy' (mostly cooperative) and 'untrustworthy' (mostly uncooperative) opponent, as well as a non-social control. Participants also a played a repeated, single-shot UG. Decisions were made on offers directed to themselves (FP), or to other players, where their decision had no effect on their own utility (TP). Participants also received offers in a non-social control condition. In the PD, MDMA increased cooperation when playing with trustworthy opponents (*OR* = 2.01 (1.46 – 2.96), $p < 0.001$), but not when playing untrustworthy opponents (*OR* = 1.25 (0.73 – 2.13)). There was no effect of MDMA on trust ratings for any opponent. When receiving feedback of the trustworthy players' decisions, MDMA increased activity in regions involved with social cognition, including the mid-cingulate gyrus, supplementary motor area, superior temporal sulcus, and bilateral insula. In the UG, MDMA reduced rejection rates of unfair offers directed at the self ($\chi^2_{(1,18)} = 11.02$, OR = 0.57, $p < 0.001$) and when making decisions in the TP condition (OR = 0.68, 95% CIs 0.51 – 0.90). No neuroimaging changes were

seen in the UG. MDMA produced clear behavioural changes in these social decision-making tasks. In the UG, our findings support previous results of reduced rejection behaviour following serotonergic manipulations. Our findings highlight the context-specific nature of MDMA-modulated mechanisms underlying decision-making in the PD. Increased engagement of social brain regions on MDMA underlies greater tolerance for untrustworthy behaviour of cooperative partners. These results suggest that alterations to the serotonin neurotransmitter system may underlie differences in how people respond to norm violations and (un)cooperative behaviour in psychiatric conditions.

4.4.2 Introduction

Section 4.2 introduced the study reported here. We sought to investigate the effect of the serotonergic compound 3,4-methylenedioxy-methamphetamine (MDMA) on social decision-making, empathy, and emotion processing. In order to do so, we carried out functional neuroimaging while participants played modified versions of the Ultimatum Game (UG) and Prisoner's Dilemma (PD). In addition, participants completed the Affective Bias task (Bland et al., 2016) and the Multifaceted Empathy Test (MET; Dziobek et al., 2008) after the scanning session.

We made the following hypotheses:

1. MDMA would reduce recognition of negative affect in the Affective Bias task.
2. MDMA would increase affective, but not cognitive, empathy in the MET.

3. In the UG, MDMA would reduce rejection rates of unfair offers directed at the participant, but not when participants responded on behalf of another player, or when responding to the game server. We hypothesised an increase in offers made during the MDMA session.
4. In the PD, participants would show more cooperative behaviour and rate their 'human' opponents as more trustworthy during the MDMA session. We hypothesised that this effect would not be present for the game server.
5. For the UG neuroimaging results, we expected to see the network of regions identified in the meta-analysis presented in Chapter 2 activated in response to unfair offers in the UG, and alterations to this as a result of MDMA administration.
6. For the PD we expected an increased activation of the social cognition areas, including the superior temporal sulcus and temporoparietal junction during the MDMA session compared to placebo.

4.4.3 Methods

4.4.3.1 Participants

21 male participants were recruited from the community and gave written informed consent to take part in the study and were financially compensated for their time. The study received ethical approval from King's College London's Psychiatry, Nursing and Midwifery Research Ethics Committee (PNM/14/15-32).

Exclusion criteria included: personal history of psychiatric illness; first-order relative with a history of psychotic illness; evidence of cardiac, hepatic, renal, gastrointestinal or neurological disorders; excessive use of caffeine and alcohol; current use of medication; failure of drugs of abuse test at screening or on either study day. Only participants with previous experience of MDMA were included in this study. Participants were only included in this study if they had at least one previous experience with MDMA. They were also required to have not used MDMA in the three months leading up to their involvement in the study. We did not collect data on lifetime use.

Due to personal circumstances, one participant withdrew from the study after his first visit. This was unrelated to his participation, and unblinding confirmed that on his first visit he received placebo. As such, 20 participants completed the study (mean age 24.8y, SD = 3.7, range = 21 – 37).

4.4.3.2 Experimental procedure

This study followed a double-blind, placebo-controlled, cross-over, counter-balanced design. Following a successful screening, participants attended two experimental study days at least one week apart (mean 9.3, SD 5.7, range 7 – 31).

See Figure 4-10 for a schematic representing the study day. Participants arrived at the study centre at 08:45, at which time we repeated physical health screening checks to confirm they were still eligible to take part. At 10:00 a pre-dose blood sample was taken to assess baseline plasma oxytocin levels. At 10:15 participants were dosed with either 100mg MDMA or placebo, orally. At

45 minutes post-dose participants gave another blood sample to assess plasma oxytocin and MDMA levels. Between these samples participants were retrained in the tasks. At 75 minutes post-dose participants entered the scanner. The scanning session lasted 90 minutes, with the first task beginning approximately 20 minutes into the session. Prior to the fMRI tasks we collected structural scans, resting state data and arterial spinal labelling data. These data are not presented in this thesis.

The timing for the MRI session was chosen because the Tmax of MDMA ranges between 1.5 – 3 hours (Kolbrich et al., 2008), and subjective effects peak and remain stable between 1 and 3 hours (Harris et al., 2002), meaning functional acquisitions would fall within these time points.

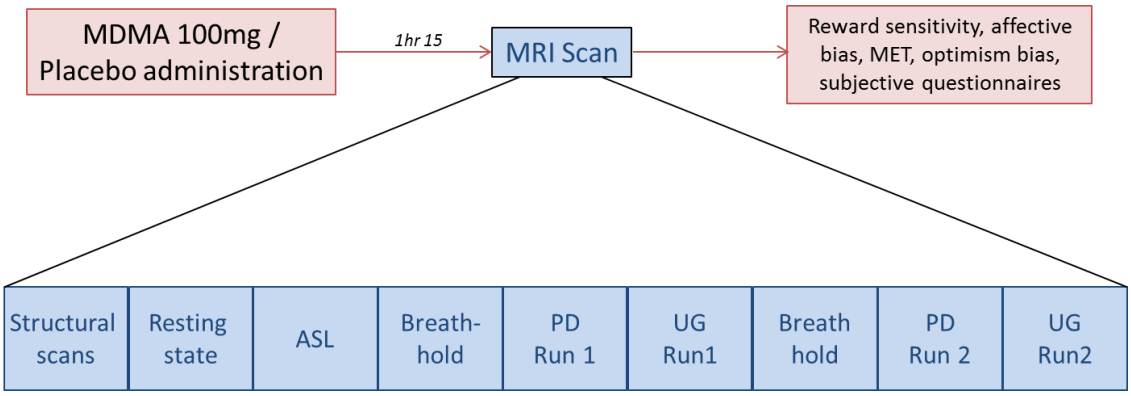


Figure 4-10: Diagram showing study timeline. ASL: arterial spin labelling

As mentioned in Section 4.3.2.2, to protect against task fatigue, each task was split into two runs. Participants first played the PD with three separate opponents (trustworthy, game server, untrustworthy) followed by a run of the

UG wherein they responded to 72 offers and were asked to make 5 offers themselves. Participants then completed a breath-hold task (results not reported here), before playing the PD again with three separate opponents (untrustworthy, game server, trustworthy) followed by the second run of the UG.

Following the scanning session, a further blood sample was taken (165 minutes post-dose, plasma oxytocin and MDMA). Participants then completed a reward sensitivity task (see below for details), the Affective Bias task, the Multifaceted Empathy Test and an optimism bias task (results not reported as part of this thesis). Participants were then discharged after the study medic was satisfied they were no longer under the influence of the drug.

The version of the PD used in the current study was described in detail in Section 4.3. The UG reported here was modified from the version described in that section, and these changes will be described next, as well as the other tasks reported in the current chapter.

Analyses of blood samples collected during this study are not reported in this thesis, due to the data not being available at the time of writing.

The Ultimatum Game

Many studies investigating the UG vary the offer proportion in relation to a fixed total stake (e.g. Civai et al., 2012; Guo et al., 2013; Kirk et al., 2011; Sanfey, 2003; Tomasino et al., 2013). While the evidence is mixed, there is data suggesting UG behaviour varies as a function of total stake, with some individuals being willing to accept a lower proportion of a high stake than a lower proportion of a low stake (Andersen et al., 2011; Novakova and Flegr,

2013; Tompkinson and Bethwaite, 1995). It could be argued that while these people still have fairness concerns, the higher utility of high-stake unfair offers takes precedent.

In order to asses if there was an effect of stake size and utility of the absolute value of the offer, we changed the offer and stake distribution from the version of the task used in the validation study (Section 4.3), while keeping all other aspects of the task the same. In line with Crockett el al (2013), we chose a range of offer values, each of which were repeated as unfair (10-20% of the total stake), fair (45-50%) and hyper-fair (80-90%) offers. By defining utility as a function of the highest absolute value offered over the course of the task, we were able to define different offers as being low utility if they were less than half of the highest offer value. In this way, not only could each offer value be presented as each of the three fairness levels, we were also able to present an equal number of high and low utility offers in each fairness condition. Appendix C has a full breakdown of the offers presented in this version of the task. In each run, there were eight unfair (10 – 20%), eight fair (45 – 50%) and eight hyper-fair (80 – 90%) offers in each condition (FP, TP, GS).

By altering this aspect of the task, it was possible to analyse whether MDMA had a differential effect on high and low utility offers. The limitation of having changed the design of the task at this stage is that it has not been evaluated for test-retest reliability. However, there has been consistently high reliability of responses displayed over two different version of this task (see 0, Section 3.3 and Section 4.3 of this chapter). Furthermore, the cover-story and presentation of the task remained unchanged from that discussed earlier in this chapter.

Therefore, while this has not yet been formally tested, the structure, presentation, instructions and hardware all remain the same as the version with high reliability.

Affective Bias task

The Affective Bias task was taken from the EMOTICOM cognitive test battery (Bland et al., 2016), and was administered approximately 195 minutes post-dose. In this task participants see a face appear on the screen for approximately half a second and are asked to indicate which emotion the face was expressing from a choice of happy, sad, fear or anger. For each emotion there are nine levels of intensity. Control conditions of faces of different ages were presented at the half way point in the task. There were 20 presentations of each emotion and 20 control faces.

Multifaceted Empathy Test

The Multifaceted Empathy Test (MET; Dziobek et al., 2011, 2008) is a task able to assess cognitive and affective empathy separately, and has been used in MDMA studies previously (Hysek et al., 2013; Kuypers et al., 2014; Schmid et al., 2014). The MET was administered approximately 180 minutes post-dose. The MET uses 40 images of people in ecologically valid, naturalistic situations. In 40 trials participants are asked to identify the emotion the person may be feeling out of a choice of four (cognitive empathy), and in 40 other trials they are asked to rate how much they empathise with the person depicted on a scale of one to nine (affective empathy). Cognitive empathy is given a score out of 40, and affective empathy is the average rating out of nine.

Reward sensitivity

In order to test if MDMA was altering participant's sensitivity to reward, they were asked to complete a modified reaction time (RT) task. In this task participants saw four circles on the screen, in the layout of the arrow buttons on a standard keyboard, within a rectangular box. On each trial a circle would be highlighted indicating that the participants should press the corresponding arrow button as quickly and accurately as possible. Trials were presented in four blocks. For the first and third block the rectangular outline was blue, and for the second and fourth block it was red. During the red block, if participants responded faster than their average RT from the previous blue block, three times in a row, a pound coin appeared on the screen to indicate they would be rewarded for their performance.

Calculating the difference in average RT between rewarded and non-rewarded blocks gave a measure of reward sensitivity, and by calculating the difference in this measure across experimental sessions we were able to ascertain whether MDMA altered reward sensitivity.

Questionnaires

We had participants fill in five subjective rating questionnaires at the end of the experimental session. Two are relevant for this thesis: the Social Value Orientation questionnaire (SVO; Van Lange, 1999) and the Social Reward Questionnaire (SRQ; Foulkes et al., 2014).

The SVO is a nine-item questionnaire which requires respondents to state preferences of resource distribution, and is a validated measure of prosociality

with good test-retest reliability (Murphy et al., 2011; Murphy and Ackermann, 2014). The SRQ is a 23-item rating scale (from strongly agree to strongly disagree) which maps onto six factors of social reward: admiration, negative social potency, passivity, prosocial interactions, sexual relationships, and sociability. These questionnaires can be found in Appendix D and Appendix E.

4.4.3.3 Behavioural statistical analyses

The Ultimatum Game

Two outcome measures were collected from this task. The first were categorical (accept or reject) responses to monetary offers. The second were continuous data of monetary offers from the participants to other players.

The categorical data were analysed using repeated-measures logistic regression, implemented with generalized estimating equations (GEE) using IBM SPSS Statistics for Windows (IBM Corp., 2012). This is a nonparametric test which takes into account the correlation of responses within subjects, and produces a chi-squared statistic (χ^2), an odds ratio (OR) and its 95% confidence interval (CI), and a *p*-value. The odds ratio represents the change in probability of an event (in this case, a rejection) occurring with a change in condition (fairness, offer origin etc.). Responses were grouped together for unfair (10 – 20% of the total stake), fair (45 – 50%) and hyper-fair (80 – 90%) offers.

In all models, participant ID was defined as the subject variable so that each participant's responses were nested together. As described in Section 4.4.3.2, there were two runs of this task to protect against task fatigue. As such it was important to test for differences across runs. Furthermore, this task was

designed to able to test for differential effects of high/low utility offers. To this end, a model was first defined testing for the main effects of utility and run. Two two-way interactions of utility*treatment and run*treatment were included in this model. The main effect of treatment was not tested in this model as the purpose of the analysis was to test for any effects of utility and run. Finally, a model was defined to test for the main effects of treatment, offer origin (FP, TP, GS), and fairness level (unfair, fair, hyper) and their three-way interaction.

In addition to the GEEs described above, each offer made by the participant was converted to a percentage of the total stake, and the average taken for each session. A paired-sample t-test was then performed to examine the difference in offer amount across experimental sessions.

The Prisoner's Dilemma

Two outcome measures were collected from this task. The first were categorical (compete or cooperate) decisions and the second were trust ratings out seven.

As with the UG, the categorical data were analysed using repeated-measures logistic regression, implemented with generalized estimating equations using IBM SPSS Statistics for Windows (IBM Corp., 2012). The odds ratio represents the change in probability of an event (in this case, a cooperate decision) occurring with a change in condition (trustworthiness, treatment etc.).

In all models, participant ID was defined as the subject variable so that each participants' responses were nested together. First, a model testing for a main effect of run and the run by treatment interaction was carried out. Following this,

a model testing the main effects of treatment and opponent (trustworthy, untrustworthy, game server), and their interaction, was analysed.

Trust ratings were collected on each round, meaning a total of 15 ratings were collected for each opponent. In order to account for uncertainty at the beginning of each game, the mean of the last eight rounds was calculated as the rating for each opponent. For each type of opponent (trustworthy, untrustworthy, game server), this was averaged across runs. I then carried out a repeated-measures ANOVA to assess differences in trust rating across opponent type and experimental session, with post-hoc pairwise comparisons carried out where appropriate.

Affective Bias

The outcome measure for this task was the percentage correct for each emotion (fear, anger, happy, sad) and the control condition. Additionally, one can calculate an 'affective bias', defined by Bland and colleagues (Bland et al., 2016) as the difference between happy and sad emotion accuracy. These outcome measures were compared across experimental sessions using repeated-measures ANOVA, followed up with post-hoc pairwise comparisons where appropriate.

Multifaceted Empathy Test

The Multifaceted Empathy Test gives the following outcome measures: a positive valence affective empathy measure, negative valence affective empathy measure, and three measures for cognitive empathy (total, positive affect, negative affect). Note that following advice from the group who created

the task, there is no pooled measure for total affective empathy (Dziobek, personal communication). Each of these was assessed with paired-samples t-tests to assess differences across experimental sessions.

Reward sensitivity

The outcome measure of this task was the mean difference in RT from the rewarded to unrewarded trials. This was compared across experimental conditions using a paired-sample t-test.

For each task, if the analysis relates to a directional hypothesis, one-tailed *p*-values will be reported, and this will be indicated.

4.4.3.4 MRI data acquisition and analysis

Functional images were acquired with a General Electric MR750 3.0 Tesla (T) MR scanner using a 32-channel head coil. A T2*-weighted echo-planar imaging sequence was used, with the following parameters: TR: 2000 ms; TE: 30 ms; flip angle: 75°; slice thickness: 3 mm; field of view: 247mm; number of slices: 41. For the Ultimatum Game, each run had 356 time points. The Prisoner's Dilemma had 282 time points per run. We also acquired a structural Magnetization Prepared Rapid Gradient Echo (MPRAGE) image with the following parameters: TR: 7312 ms; TE: 3.02 ms; flip angle 11°; slice thickness: 3 mm; 196 sagittal slices; field of view = 270mm.

Data were pre-processed and analysed using SPM12 (Wellcome Department of Cognitive Neurology, London). Prior to first level modelling, fMRI data were reoriented, slice time-corrected and realigned initially to the first image and then

to the mean image. These were then co-registered to the T1 structural file. The structural data were segmented to aid special normalisation and a common group-specific template was created using DARTEL registration (Ashburner, 2007). The functional files were then normalised to the MNI template using deformation flow fields and structural template created through DARTEL. Finally, functional images were smoothed using an 8mm FWHM Gaussian kernel.

The first and second level analyses are described separately for the Ultimatum Game and Prisoner's Dilemma below.

The Ultimatum Game

Both runs of the task were included in a single GLM first level model. Ten conditions of interest were defined. Nine of these made up the periods where participants were presented with the offer, and included each combination of offer definition (unfair, fair, hyper-fair) and condition (first person, third party, game server). Onsets were defined as the moment the offer appeared on the screen, with a duration of 3 seconds (the time the offers remained on the screen). The tenth condition contained the periods participants were asked to make an offer, with a duration of seven seconds. Seven movement parameters (six standard parameters as well as volume-to-volume movement) were included as regressors of no interest. Volumes where the volume-to-volume movement exceeded 1mm, as well the volume before and after, were also modelled as regressors of no interest. The decision button press was also modelled as a condition of no interest with duration of zero.

At the second level, three 2x2, flexible factorial ANOVA models were conducted, first as a whole brain analysis, then with small volume correction (SVC) using a mask produced from the meta-analysis reported in 0 (Gabay et al., 2014).

The first flexible factorial was modelled to ascertain if the current study could replicate findings in the literature during the placebo session in terms of differences between responding to social (first person) or non-social (game server) players, and the difference between fair and unfair offers. The two main effects and the interaction were modelled. The first person condition was chosen to represent the social condition as this is the more common contrast investigated in the literature.

The second model was designed to investigate any treatment effects on neural responses to fair and unfair offers in the first person condition. The main effect of treatment, the main effect of fairness, and their interaction were modelled.

The third model investigated any differences between responding for the self or for a third party, and the treatment effect on these differences. The main effect of treatment, the main effect of offer origin (FP or TP) and their interaction were modelled.

In addition to these, a paired-samples t-test was conducted to examine any differences in neural correlates of making an offer across treatment sessions.

The Prisoner's Dilemma

Both runs of the task were included in a single GLM first level model. A simple model was defined with each condition (trustworthy, untrustworthy, game server opponents) by trial period (decision, feedback, trust rating) combination. The decision and feedback periods were defined with durations of three seconds and the trust rating with five seconds duration. As with the UG, seven movement parameters (six standard parameters as well as volume-to-volume movement) were included as regressors of no interest. Volumes where the volume-to-volume movement exceeded 1mm, as well the volume before and after, were also modelled as regressors of no interest

At the second-level, a series of whole-brain analyses were carried out. First, three one-way repeated-measures ANOVAs were carried out on the placebo session data to examine differences in activation across opponents for each of the time periods (decision, feedback, trust rating).

Next, a series of paired-samples t-tests were carried out, investigating any differences across experimental sessions for each time period (decision, feedback, trust rating) and each opponent type (trustworthy, untrustworthy, game server).

4.4.4 Results

4.4.4.1 Ultimatum Game behavioural results

The figures in this section present boxplots of the ultimatum game rejection behaviour. It should be noted that while the statistical analysis of these results take into account responses of each trial, the data are represented in the figures as rejection *rates*, as these are more intuitively represented graphically.

For one participant, the task did not run properly during scanning, rendering his data for this task unusable. As such, the analyses in this section are based on N = 19.

Placebo session rejection behaviour

In this section I will present the placebo session data to confirm that the task produces results in line with the version of the task validated in Section 4.3 and the literature. While the study presented in Section 4.3 validated the task, the version in this section had the addition of changes in overall stake size.

Figure 4-11 displays the rejection rates for the placebo session across conditions. There was a main effect of both offer origin and fairness level (respectively: $\chi^2_{(1,18)} = 7.35$, $p = 0.025$; $\chi^2 = 63.65$, $p < 0.001$), with no statistically significant interaction. Compared to unfair offers, there was a lower probability of rejection of fair and hyper-fair offers (respectively: $\chi^2_{(1,18)} = 25.94$, OR = 0.01 95%CIs 0.002 – 0.07, one-tailed $p < 0.001$; $\chi^2_{(1,18)} = 13.23$, OR = 0.03, 95%CIs 0.003 – 0.18, one-tailed $p < 0.001$). There was no statistical difference in rejection rates for fair versus hyper-fair offers ($\chi^2_{(1,18)} = 0.63$, OR =

3.10, 95%CIs 0.19 – 50.67, p = 0.428). There was a statistically significant reduction in the probability of rejection in the game server condition compared to the first person condition ($\chi^2_{(1,18)}$ = 15.60, OR = 0.20, 95%CIs 0.09 – 0.45, one-tailed p < 0.001). Similarly, there was a decrease in the probability of rejection in the game server condition compared to the third party condition ($\chi^2_{(1,18)}$ = 14.17, OR = 0.22, 95%CIs 0.10 – 0.48, one-tailed p < 0.001). There was no statistical difference between first person and third party decisions ($\chi^2_{(1,18)}$ = 0.52, OR = 0.894, 95%CIs 0.66 – 1.21, one-tailed p = 0.471).

The effect of run and utility on rejection behaviour

In order to assess if it is appropriate to combine data across runs within each session and across utility categories (i.e. combine all stake sizes), this section assesses the effects of run and utility, as well as their interaction with treatment.

Figure 4-12A displays the overall rejection rates for each run in both experimental sessions. Figure 4-12B displays rejection rates for high and low utility in both experimental conditions, combined across runs. A GEE analysis showed that there was no effect of run or utility (respectively: $\chi^2_{(1,18)}$ = 1.00, OR = 0.87, 95%CIs 0.67 – 1.14, p = 0.319; $\chi^2_{(1,18)}$ = 3.05, OR = 0.86, 95%CIs 0.73 – 1.02, p = 0.081), although utility did approach statistical significance, such that there was a lower probability of rejecting high utility offers than low utility offers. Neither run nor utility showed a statistically significant interaction with treatment (ps > 0.25).

These results confirm that it is appropriate to combine data across within-session runs. Additionally, as the effect of utility did not reach statistical significance, the remaining analyses will include all stake sizes.

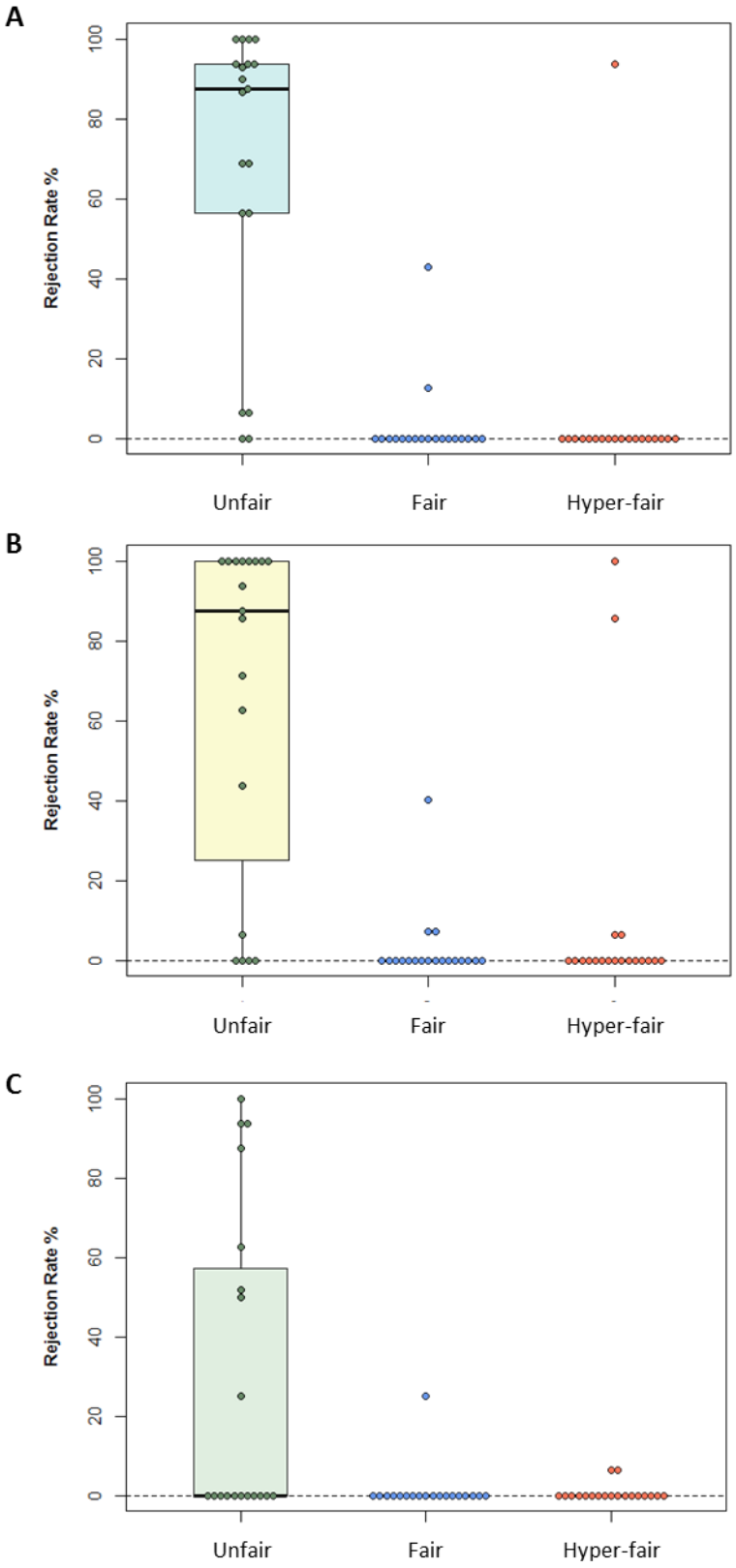


Figure 4-11: Boxplots displaying rejection rates across conditions in the placebo session. A) First person, B) Third party, C) Game server

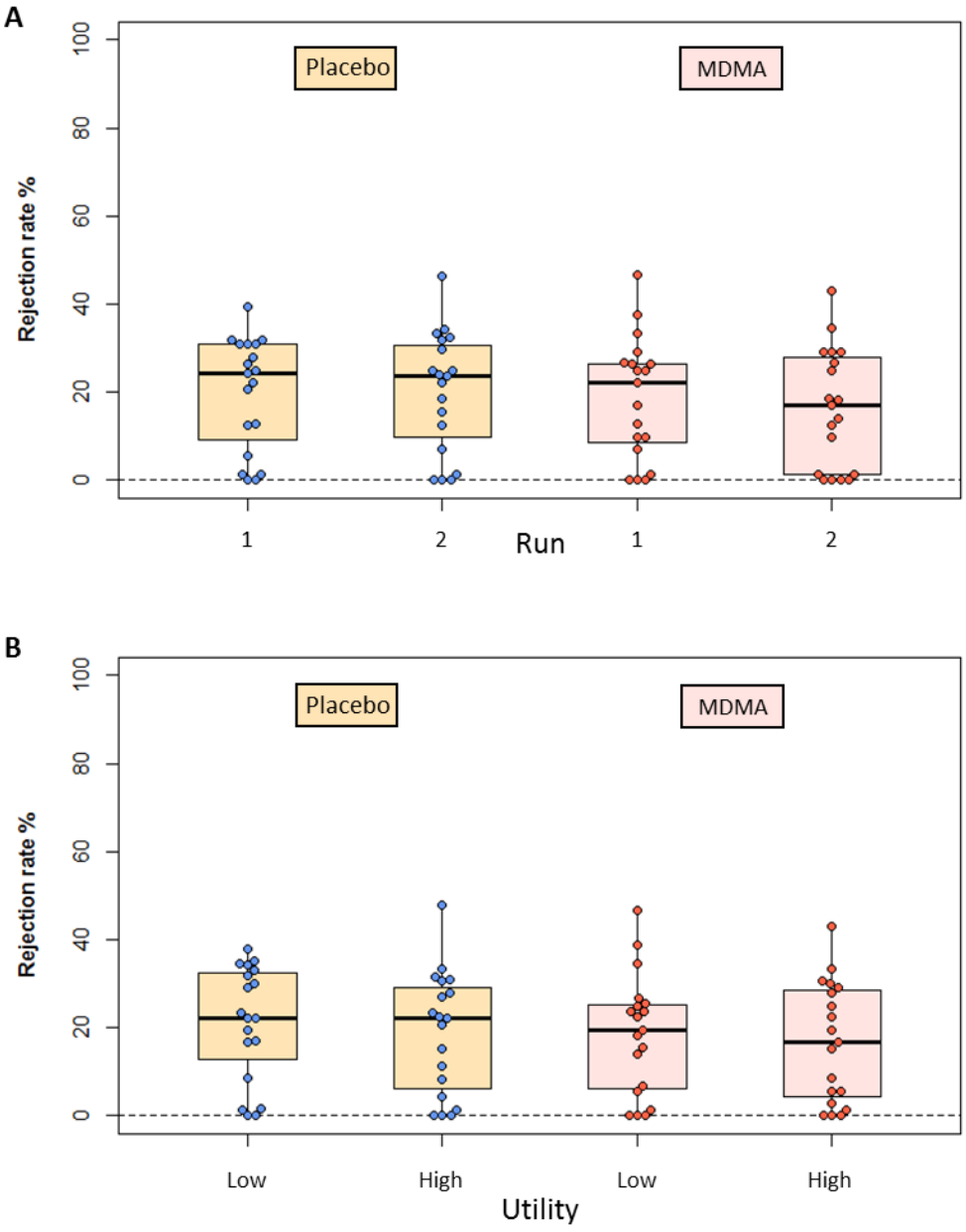


Figure 4-12: Boxplots of rejection rates across all conditions, separated by A) run and B) high/low utility

The effect of MDMA on the Ultimatum Game

Figure 4-13 displays the rejection rates across conditions and treatment sessions, as well as the change in rejection rate for each offer level across treatment sessions.

A GEE analysis found no main effect of treatment (p = 0.888), but a main effect of offer origin, fairness, and a three-way treatment by fairness by offer origin interaction (all ps < 0.009). Closer examination of the parameter estimates revealed the following. There was a lower probability of rejecting unfair offers in the first person condition under the influence of MDMA compared to placebo ($\chi^2_{(1,18)}$ = 11.02, OR = 0.57, 95%CIs 0.41 – 0.80, one-tailed p < 0.001). The same effect of MDMA was found in the third party condition (OR = 0.68, 95%CIs 0.51 – 0.90). There was no statistical difference between these two effect sizes (p = 0.254). No effect of treatment was seen for unfair offers from the game server (OR = 0.85, 95%CIs 0.56 – 1.30), indicating a significant interaction (p = 0.034). There were no other statistically significant treatment effects on rejection behaviour in the UG.

A paired t-test revealed a statistically significant increase in average percentage offer from the participants during the MDMA session compared to the placebo session (placebo mean offer = 48.2%; MDMA mean offer = 55.7%); mean difference = 7.5, SD = 10.25, $t_{(18)}$ = 3.17, one-tailed p = 0.003, Cohen's d = 0.82). Morris and DeShon (2002) recommend a correction to Cohen's d calculations based on the correlation between scores when using a repeated-measures design intended to assess treatment effects across a sample, and

this correction has been used here. The correlation of mean offer level across experimental sessions was $r = 0.79$.

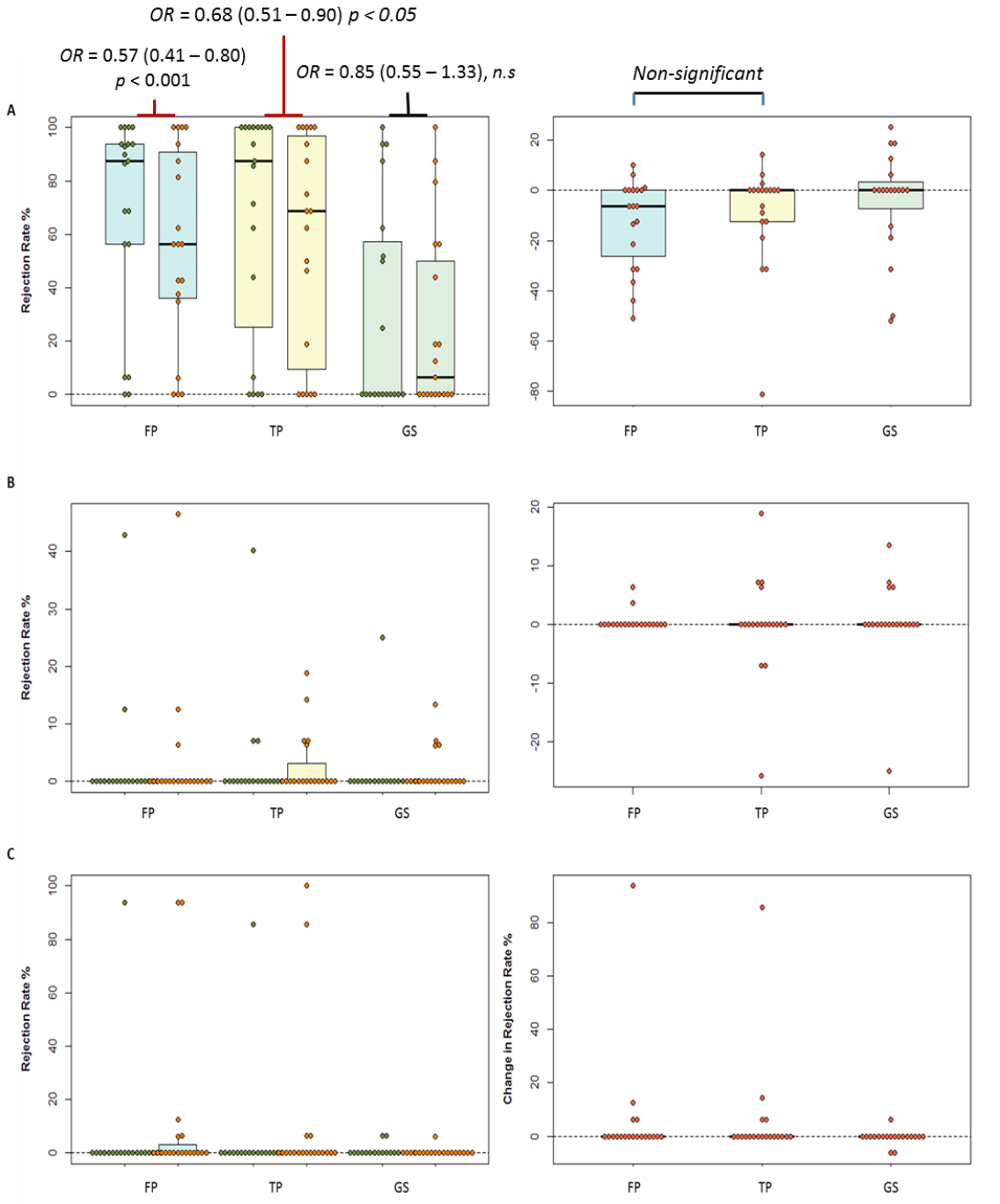


Figure 4-13: Boxplots displaying rejection rates. The left column displays both the placebo session (green dots) and MDMA session (orange dots) for each condition. The right column represents the change in rejection rate from placebo to MDMA session. A) Unfair offers, B) Fair offers, C) Hyper-fair offers Ultimatum Game fMRI results

4.4.4.2 Ultimatum Game fMRI results

Placebo session

The first fMRI analysis was designed to assess the task effects in the placebo condition. A flexible factorial model was defined with fairness (fair, unfair) and offer origin (first person, game server) as within-subject factors.

There were no statistically significant clusters (threshold of $p < 0.05$ FWE-corrected) in the main effects of fairness or offer origin,or interaction contrasts. This was true for the whole-brain analysis and the small volume corrected (SVC) analysis using the mask obtained from the meta-analysis carried in 0.

The effect of MDMA on the neural correlates of unfairness

In order to assess the effect MDMA on the neural correlates of receiving unfair offers, a flexible factorial model was defined with fairness (fair, unfair) and treatment (placebo, MDMA) as within-subject factors. This analysis was restricted to the first person condition.

In the whole brain analysis there was a main effect of fairness (see Table 4-6 and Figure 4-14), such that when compared to receiving unfair offers, fair offers produced higher activation in the posterior superior temporal gyrus. There was no main effect of treatment nor an interaction. There were no significant clusters when the same analysis was performed with SVC.

The effect of social partner

In order to assess differences in neural effects of receiving offers directed at the self or a third party a flexible factorial model was defined with treatment (placebo, MDMA) and offer origin (first person, third party) as factors. This analysis was restricted to unfair offers, as we had hypothesised a difference in rejection rates of unfair offers between first person and third party conditions.

There were no main effects or an interaction for both the whole brain analysis and the SVC analysis.

Table 4-6: fMRI activations in the fairness by treatment 2x2 flexible factorial model, restricted to the FP condition. Regions identified by the Harvard-Oxford probabilistic atlas (Desikan et al., 2006)

Cluster level			Peak level				
			MNI				
Region	**FWE-corr *p*-value**	**Cluster size**	***x***	***y***	***z***	***z*-value**	
Main effect of fairness							
Posterior superior temporal gyrus	0.006	228	63	-16	2	4.13	Posterior superior temporal gyrus
			66	-28	5	4.00	
			57	-1	2	3.78	Plarum polare

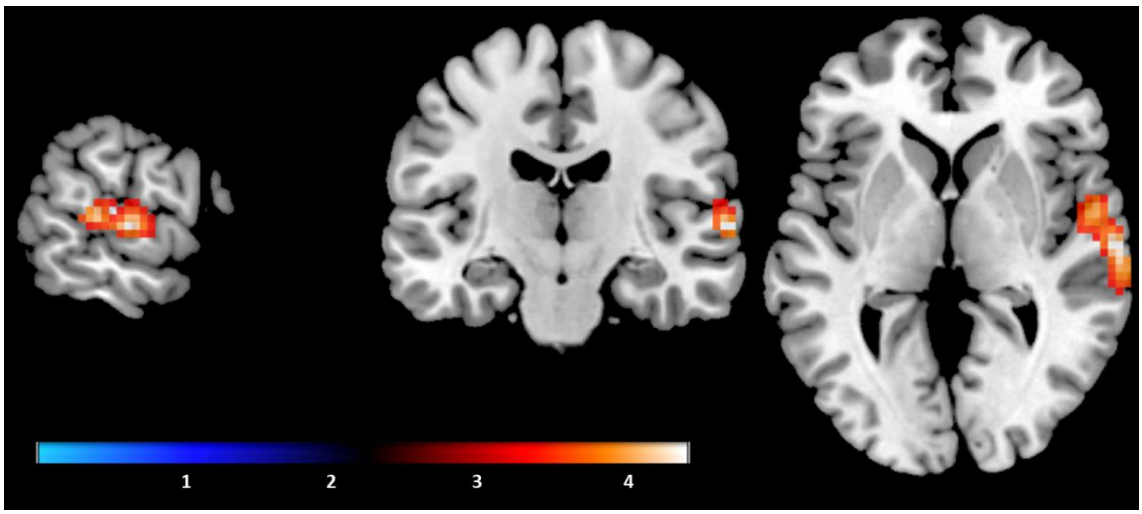


Figure 4-14: Main effect of fairness in treatment x fairness ANOVA restriced to FP condition. Colour bar represents Z values. Image thresholded at height threshold of FEW-corrected $p < 0.05$

As the meta-analysis in 0 suggested, there are robust findings in the literature regarding the neural correlates of receiving unfair offers in the UG (Gabay et al., 2014) and our task was based on those presented in the meta-analysis. These include increased activation in the insula, medial prefrontal cortex (mPFC) and the cingulate gyrus. Given the strong behavioural results, both in the placebo condition alone as well as the effect of MDMA, it is surprising that significant clusters were only found in one analysis, and that none of these were in the hypothesised regions. Appendix F details a set of analyses carried out on the placebo data to further explore this data.

4.4.4.3 Prisoner's Dilemma behavioural results

All analyses in this section are based on N = 20.

Trust ratings

Figure 4-15 displays the mean trust rating for each type of opponent across experimental sessions. A 2 (treatment: placebo, MDMA) x 3 (Trustworthiness: trustworthy, untrustworthy, game server) repeated-measures ANOVA revealed a main effect of trustworthiness ($F_{(2,38)}$ = 25.39, p < 0.001, $ή^2$ = 0.57), but no main effect of treatment, nor an interaction (respectively: $F_{(1,19)}$ = 1.53, p = 0.232, $ή^2$ = 0.07; $F_{(2,38)}$ = 0.08, p = 0.928, $ή^2$ < 0.01). Post-hoc pairwise comparisons found a statistically significant difference in trust ratings between trustworthy and untrustworthy opponents (mean diff = 2.8, 95% CIs 1.9 – 3.6, p < 0.001) and between trustworthy and game server opponents (mean diff = 1.8, 95% CI 0.6 – 3.0, p = 0.003). The difference between untrustworthy and game server opponents did not reach statistical significance (mean diff = 1.0, 95% CI -0.04 – 2.05, p = 0.063). All p-values reported here are Bonferroni-corrected.

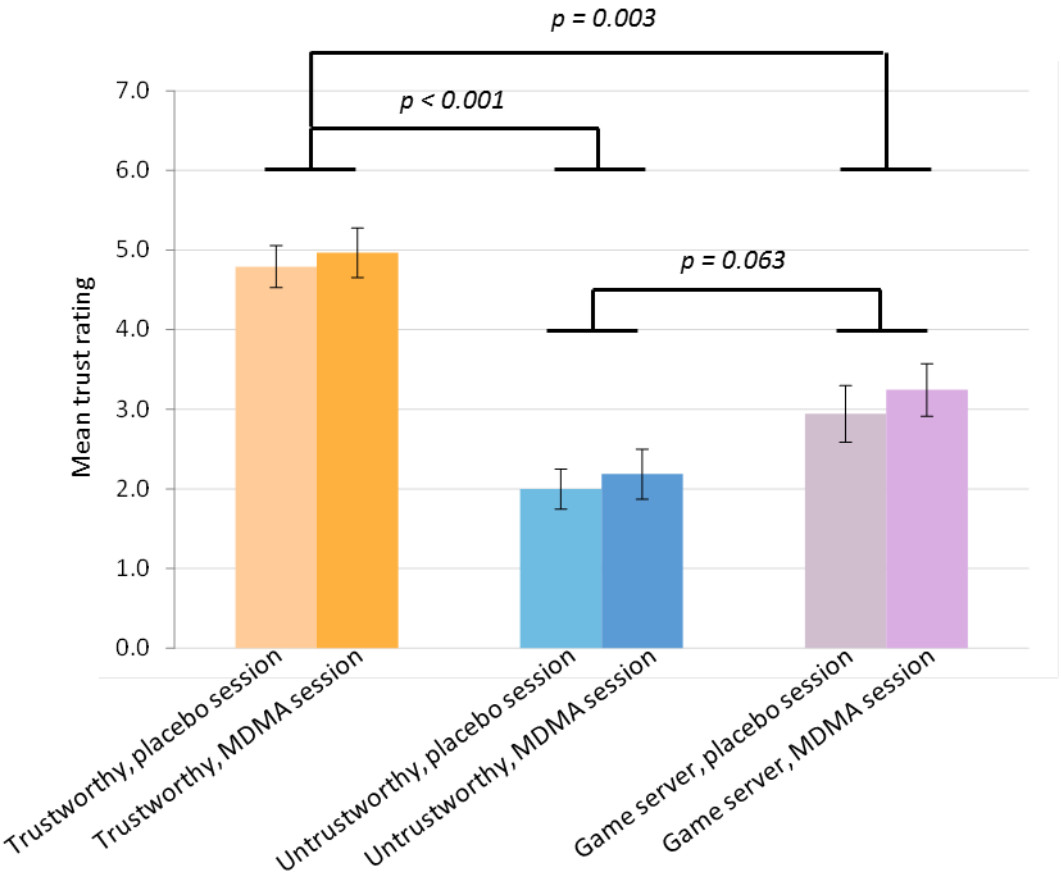


Figure 4-15: Barplots displaying the mean trust rating for each opponent type across experimental sessions. All *p*-values are Bonferroni-corrected. Error bars: ±1SE

Cooperative behaviour

First, I carried out an analysis to assess the impact of completing the task across two runs. A GEE analysis tested the main effect of run and its interaction with treatment session. No main effect of run was found, but there was a treatment by run interaction (respectively: $\chi^2_{(1,19)} = 0.26$, $p = 0.614$; $\chi^2 = 7.70$, $p = 0.021$), such that there was an increase in the probability of a cooperate decision in the second run during the MDMA session compared to the first run

(OR = 1.28, 95% CIs 1.01 – 1.58). This may reflect a change in subjective effects of the drug. However, since the effect is restricted to this treatment session, the following analyses will combine data across runs.

Figure 4-16 displays the percentage of cooperate decisions when playing each opponent, across treatment sessions.

There was a statistically significant main effect of treatment, trustworthiness and their interaction (all *p*s < 0.005). MDMA increased the probability of a cooperative decision when playing a trustworthy player ($\chi^2_{(1,19)}$ = 15.33, OR = 2.01 95% CI 1.42 – 2.84, $p < 0.001$), but *not* when playing an untrustworthy player (OR = 1.37 95% CI 0.78 – 2.30) or the game server (OR = 1.03 95% CI 0.71 – 1.48).

In order to further explore this, the data were plotted on a round-by-round basis (see Figure 4-17). Since the positioning of the opponents decisions were jittered across runs, each run was truncated by one decision. An example of this is shown in Figure 4-17A. For each round, each participant was scored with either a zero (if they had competed at this point on both runs of the session), a one (if they had cooperated on both runs), or 0.5 (if they had competed on one run and cooperated on the other). For each round, this was then averaged across participants, giving a mean proportion of cooperative decisions for each round with each type of opponent.

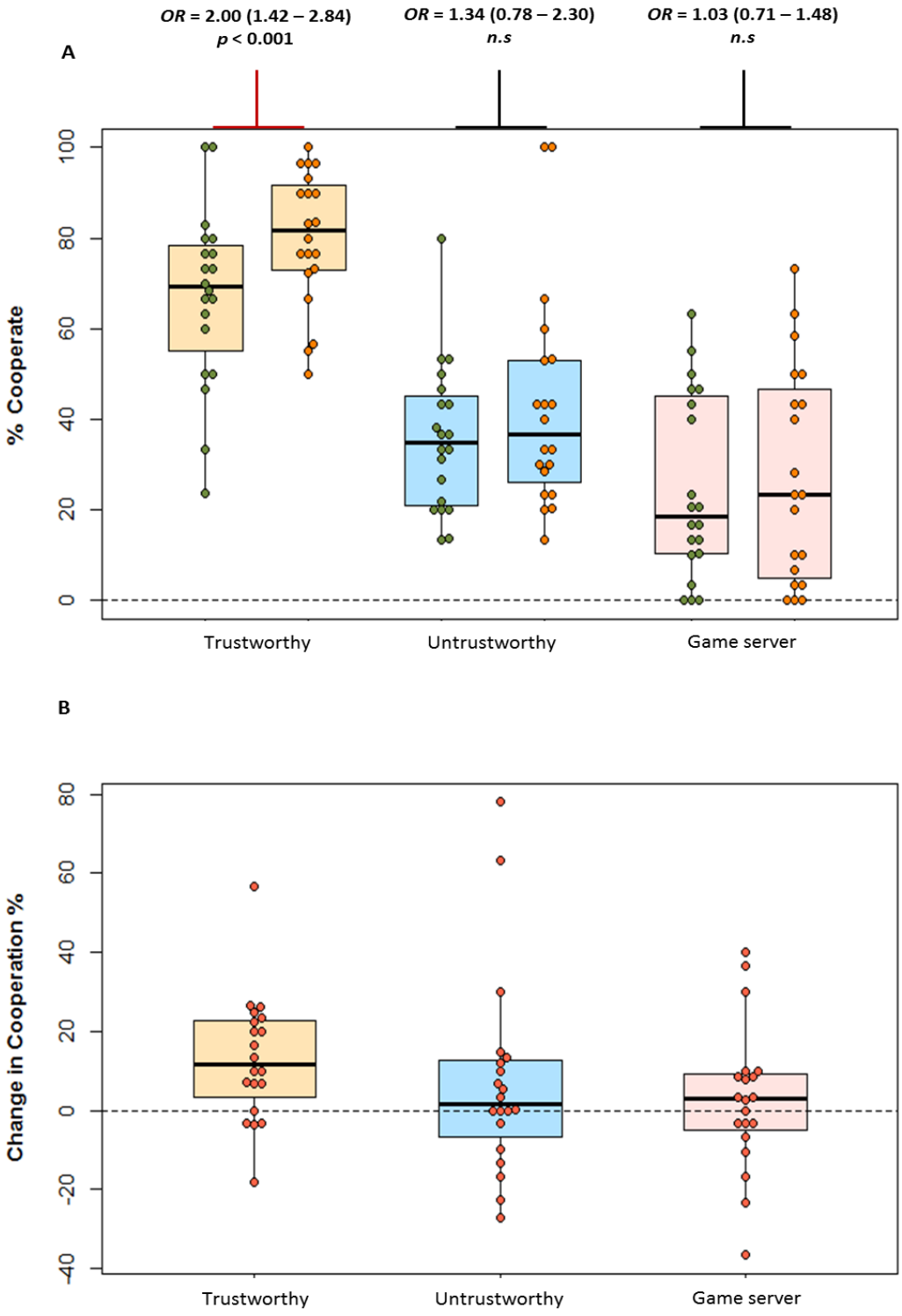


Figure 4-16: Boxplots displaying A) Prisoner's Dilemma Cooperation rates with each type of opponent. Green dots: placebo session, orange dots: MDMA session. B) Change in rates of cooperation from placebo to MDMA. NB: These plots present the percentage of cooperate decisions because they are graphically intuitive. The analysis described in this section is not based on proportions, but is a logistic regression implemented by GEE, using the trial-by-trial data.

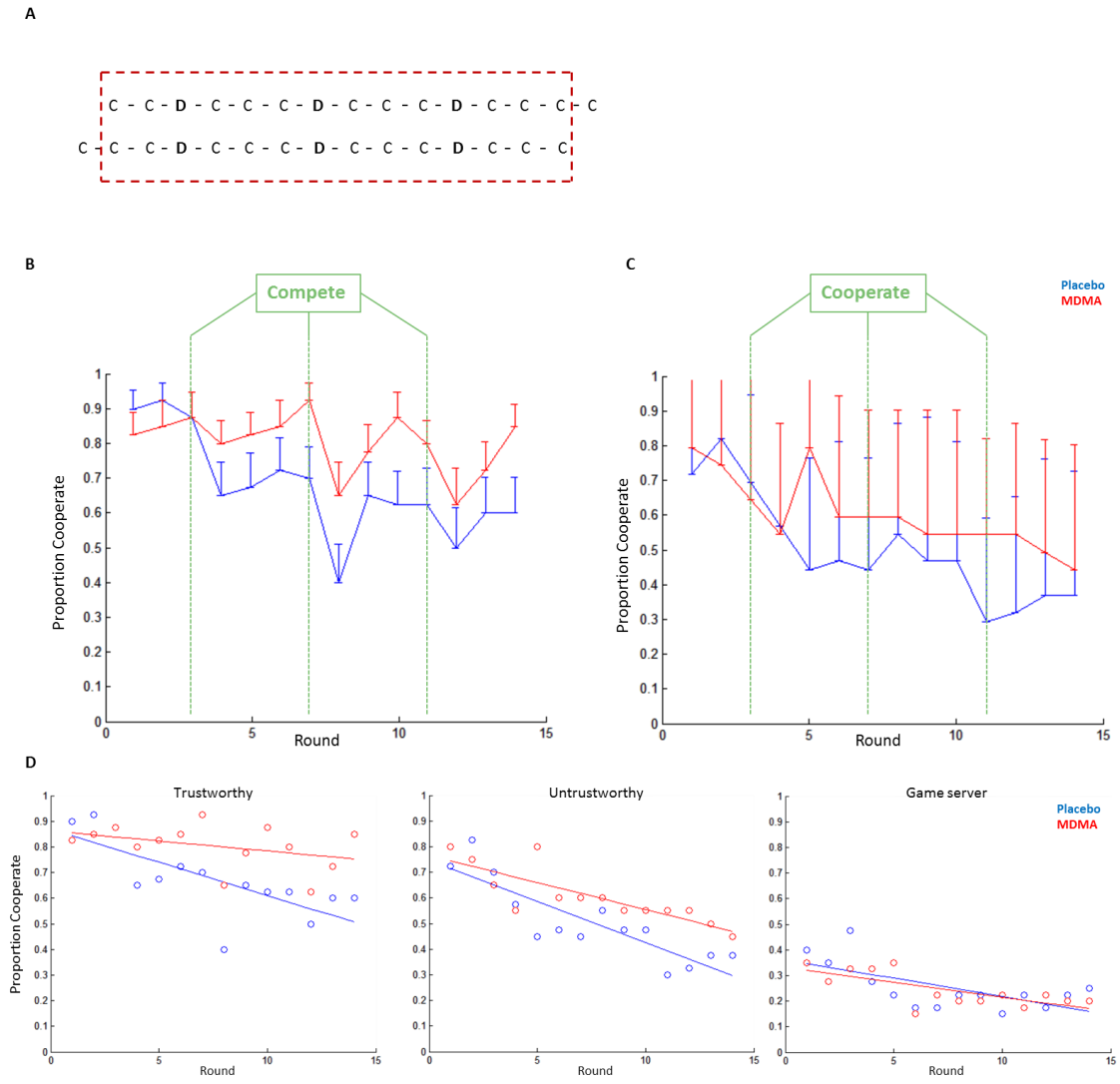


Figure 4-17: Breaking down PD behaviour trial by trial. A) Lining up decisions across runs: in order to account for the jitter in opponent responses the last trial of the first run and first trial of the final run were removed. 'C' indicates where opponents were congruous with their trustworthiness. 'D' indicates where they deviated from this. B) Proportion of cooperate decisions on each round, averaged across participants, for the trustworthy opponent. C) Proportion of cooperate decisions on each round, averaged across participants for the untrustworthy opponent. D) Proportion of cooperate decisions on each round plotted as scatterplots with the line of best fit for each session; for the trustworthy opponent, there is a steady decline in cooperative decisions during the placebo session, which does not occur during the MDMA session (see text below; GEE round-by-experimental session interaction: $\chi^2_{(1,19)}$ = 16.79, OR = 1.08, 95% CI 1.043 – 1.13, p < 0.001). Error bars: ±1SE

With visual examination of Figure 4-17B and C, it is clear that there is much greater variation in how participants behaved in the untrustworthy condition compared with the trustworthy condition. Furthermore, Figure 4-17C shows a steady decline in cooperation over the course of the game with untrustworthy

opponents in both experimental sessions. Visual inspection of Figure 4-17B shows that following the first decision to compete by the usually trustworthy opponents, participants consistently cooperated more in the MDMA session than the placebo session. Furthermore, while there are clear effects of the decisions to compete, it looks feasible that the overall steady decline in cooperation over rounds of the game may differ across sessions in this condition. This is represented in Figure 4-17D, which plots the points in Figure 4-17B and C as a scatterplot, with a line of best fit running through these points.

To test this statistically, a different model was analysed in the GEE framework. Restricting the analysis to each opponent in turn (trustworthy, untrustworthy, game server), the round number was included as a covariate, and the main effect of round as well as the round-by-experimental session interaction were modelled. This is the equivalent of statistically comparing the beta coefficients to assess a difference in the slope of a relationship in a parametric regression; but here it is for repeated-measurements of binary decision data. Again, it is important to note that the visual representations presented here show proportions of cooperate decisions for 14 of the 15 rounds, whereas the analysis is based on trial by trial binary responses for all trials.

For all three opponents there was a statistically significant main effect of round such that there was a decreased probability of a cooperate decision as the game progressed (trustworthy: $\chi^2_{(1,19)} = 15.06$, OR = 0.90, 95% CI 0.87 – 0.93, $p < 0.001$; untrustworthy: $\chi^2_{(1,19)} = 48.04$, OR = 0.84, 95% CI 0.79 – 0.89, $p < 0.001$; game server: $\chi^2_{(1,19)} = 8.41$, OR = 0.94, 95% CI 0.90 – 0.97, $p = 0.004$). Only for the trustworthy opponent was there a round-by-session interaction (χ

$^{2}_{(1,19)}$ = 16.79, OR = 1.08, 95% CI 1.043 – 1.13, $p < 0.001$). Whilst the effect size here is small, it suggests that, as seen in Figure 4-17D, the effect of MDMA seen in the main analysis may be understood as a maintained level of overall cooperation for the duration of the game with this opponent, which is not seen in the placebo session.

The relationship between trust and cooperative behaviour

In order to assess the relationship between trust and cooperative behaviour, a new GEE model was defined. In this model, treatment and opponent were defined as factors, and the previous round's trust rating was defined as a continuous covariate. The model was tested for the main effect of the covariate and the covariate-by-treatment interaction.

There was a main effect of previous trust rating on decision ($\chi^{2}_{(1,19)}$ = 68.31, $p <$ 0.001). There was no treatment by previous trust rating interaction ($\chi^{2}_{(1,19)}$ = 1.89, p = 0.170). This indicates that across conditions, controlling for correlations between repeated measurements, the greater the previous round's trust rating, the greater the probability of a cooperate decision. The lack of interaction effect shows that this relationship was not affected by treatment session.

4.4.4.4 Prisoner's Dilemma fMRI results

Placebo session

No effects were found (threshold of FWE-corrected $p < 0.05$) in three one-way, within-subject ANOVAs, looking at the effect of opponent type (trustworthy,

untrustworthy, game server) on each period of the trial (decision, feedback, trust rating).

The effect of MDMA

Paired-sample t-tests revealed no differences in neural activity across experimental sessions for the decision period or trust rating period, regardless of opponent type. The same was true of the feedback period for untrustworthy opponents and the game server.

During the feedback period when playing a trustworthy opponent, there was increased activation during the MDMA session in the following clusters (see Table 4-7 and Figure 4-18): i) two clusters encompassing bilateral central opercular cortex/posterior insula. On the left this cluster has a peak in the inferior frontal gyrus, pars triangularis. Bilaterally this cluster extends to the anterior insular, and on the right the putamen; ii) bilateral mid-cingulate cortex, extending into the supplementary motor area; iii) a cluster encompassing the right posterior superior temporal sulcus and lateral occipital cortex.

Participants received feedback that the other player cooperated on 12 out of 15 rounds when playing the trustworthy opponent, and feedback that they had competed 3 of the 15 rounds. In order to assess what was driving the difference in activation in this condition across sessions, a new first level model was defined with onsets of cooperative feedback and competitive feedback defined separately. At the second level, the effect of treatment was assessed with a paired-sample t-test. It is acknowledged that the low number of competitive feedback trials would not allow a clear determination of their contribution and

therefore the analysis on the cooperate trials were considered confirmatory if the results overlapped, or were greater. When comparing just the rounds with cooperative feedback, there was a large overlap of these increased activations. This suggests that these results were due to MDMA-induced changes in response to cooperative rather than competitive feedback. When removing the competitive feedback, the clusters became larger – of particular note was an increase in size of the activation of the right putamen.

Table 4-7: fMRI activations in the for the PD. Regions identified by the Harvard-Oxford probabilistic atlas (Desikan et al., 2006)

Cluster level			Peak level				
			MNI				
Region	**FWE-corr *p*-value**	**Cluster size**	***x***	***y***	***z***	***z*-value**	
MDMA > placebo, Feedback period with the trustworthy opponent							
Left inferior Frontal gyrus	< 0.001	356	-52	22	7	5.14	Inferior frontal gyrus
			-49	-15	17	4.49	Central operculum
			-45	-22	20	4.41	
Right central operculum	< 0.001	388	52	-4	-3	4.02	Planum polare
			45	-22	17	3.91	Parietal operculum
			45	8	0	3.86	Central operculum
Mid-cingulate cortex	0.001	231	-11	-8	40	4.56	Mid-cingulate sulcus
			15	-26	43	3.90	
			4	-11	59	3.81	Supplementary motor area
Posterior superior temporal sulcus	0.004	176	45	-64	3	4.16	Posterior superior temporal sulcus
			60	-34	3	3.82	
			45	-60	13	3.46	

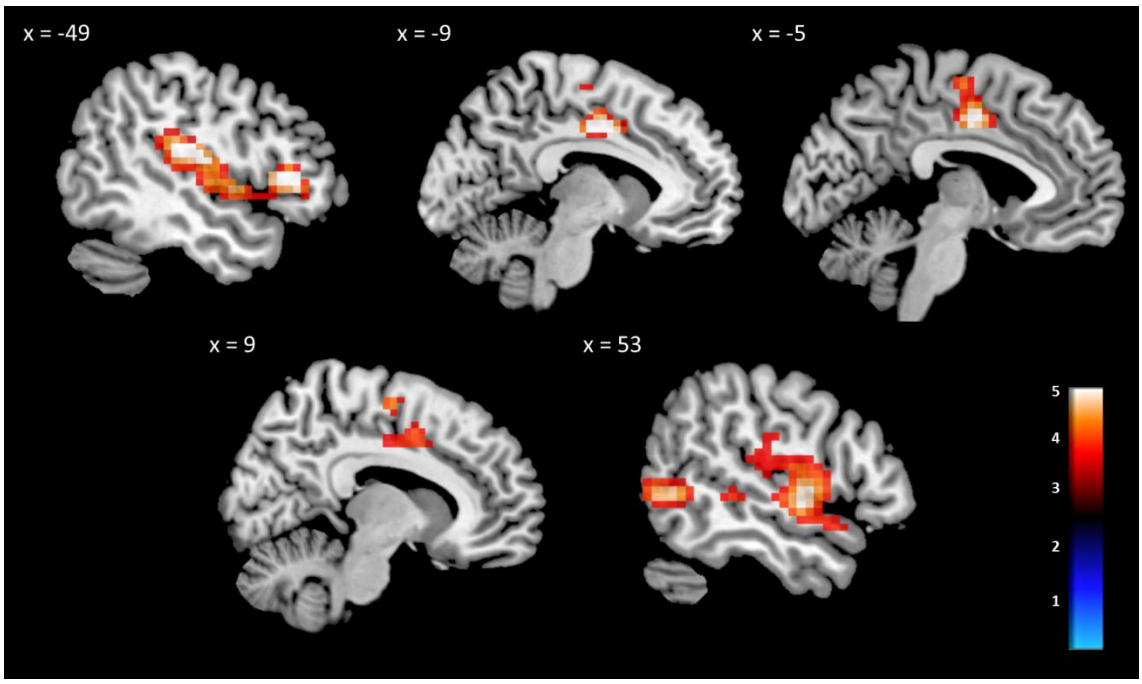


Figure 4-18: Increased activations in the MDMA compared to placebo session when receiving feedback from the trustworthy opponent. Colour bar represents Z values. Image thresholded at FWE-corrected $p < 0.05$

4.4.4.5 Affective Bias

The Affective Bias task examined facial affect recognition across four different emotional states: happy, sad, fear, anger. There was a control condition of assessing which of four age-groups a face belonged. The results from this task are displayed in Figure 4-19.

A paired-sample t-test showed no effect of treatment on the control condition (mean difference = -4.8, SD = 12.6, $t_{(17)}$ = -1.64, p = 0.120). This shows that MDMA did not alter participants' ability to recognise and make judgments on faces in general. A 2 (treatment: placebo, MDMA) x 4 (emotion: happy, sad, fear, anger) repeated-measure ANOVA found a no main effect of treatment

($F_{1,17)}$ = 2.56, p = 0.128, $ή^2$ = 0.13), but both a main effect of emotion ($F_{3,51)}$ = 29.22, p < 0.001, $ή^2$ = 0.63) and a treatment*emotion interaction ($F_{1,17)}$ = 3.56, p = 0.029, $ή^2$ = 0.16).

Post-hoc comparisons found that participants were more accurate in identifying happy emotions when compared to all others (all Bonferroni-corrected ps < 0.003); anger was identified less accurately than all other emotions (all Bonferroni-corrected ps < 0.001); there was no difference in accuracy in identifying sad compared to fearful faces. The interaction appears to be driven by a reduced accuracy in identifying fear and anger during the MDMA session compared to the placebo (see

Table 4-8). Bland et al (2016) define the affective bias as being the difference in accuracy between happy and sad emotions. A paired-sample t-test found no statistical difference in affective bias across treatment sessions ($t_{(18)}$ = -0.18, p = 0.863).

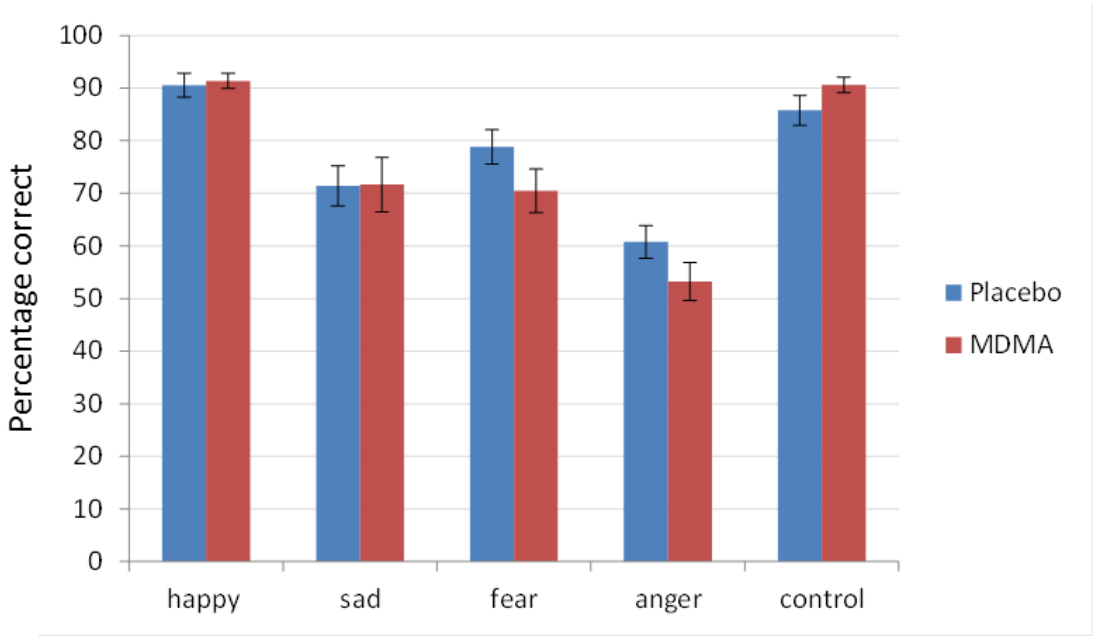


Figure 4-19: Barplot displaying results from the Affective Bias. Error bars: ±1SE

Table 4-8: Post-hoc paired t-tests comparing facial affect recognition across experimental sessions for each emotion

Emotion	Mean difference, % (MDMA-placebo)	Std deviation	$t_{(17)}$	Uncorrected-*p*
Happy	0.8	10.9	-0.325	0.749
Sad	0.2	14.5	-0.069	0.946
Fear	-8.3	16.0	2.211	0.041
Anger	-7.5	14.2	2.246	0.038

4.4.4.6 The Multifaceted Empathy Test

The Multifaceted Empathy Test gives the following outcome measures: a positive valence affective empathy measure, negative valence affective empathy measure, and three measures for cognitive empathy (total, positive affect, negative affect). Unfortunately we had missing data for five participants for the affective empathy, and four participants for cognitive empathy; therefore these analyses are based on N = 15 and N = 16, respectively. Figure 4-9 displays the mean and standard deviation for each of these outcome measures.

Paired-samples t-tests show that there were no differences across treatment sessions for any comparison across treatment sessions (all *p*s > 0.193).

Table 4-9: Mean (SD) of the MET scores

	Placebo	**MDMA**
Cognitive empathy		
All stimuli	29.07 (2.84)	29.0 (3.14)
Positive stimuli	15.53 (1.19)	15.20 (1.74)
Negative stimuli	13.53 (2.53)	13.80 (2.57)
Affective empathy		
Positive stimuli	5.57 (1.24)	6.03 (0.83)
Negative stimuli	4.68 (1.93)	4.63 (2.27)

4.4.4.7 Reward sensitivity

This task was designed to establish if MDMA altered participants' sensitivity to reward. The task produced reaction time (RT) measurements for rewarded and unrewarded trials. A repeated-measures ANOVA showed that there was a main effect of trial type such that in both experimental sessions participants' responded faster for the rewarded trials compared to the unrewarded trials (mean diff = -77.52ms, $F_{(1,19)} = 8.04$, one-tailed $p = 0.006$, $ή^2 = 0.30$). There was no main effect of treatment session, nor a session by trial type interaction (respectively: mean diff = -4.93, $F_{(1,19)} = 0.28$, one-tailed $p = 0.603$, $ή^2 = 0.12$; $F_{(1,19)} = 0.021$, one-tailed $p = 0.888$, $ή^2 < 0.01$).

While there was no change in mean 'reward sensitivity' (the difference in RT between rewarded and unrewarded blocks), it is worth assessing whether the variance in the change in reward sensitivity could account for the findings in the UG and PD (although it should be noted that the PD involved non-monetary rewards). To this end, I carried out two bivariate correlation analyses. There was no significant correlation of the change in reward sensitivity with the change in rejection rates in the FP condition of the UG ($r = 0.02$, $p = 0.924$) or with the change in cooperation rates when playing trustworthy opponents in the PDG ($r = -0.03$, $p = 0.897$).

These results show that participants were sensitive to reward, willing to put more effort into improving their reaction time in the rewarded trials, but that MDMA did not increase or decrease this sensitivity to reward.

4.4.4.8 Questionnaires

Social Value Orientation

The SVO (Van Lange, 1999) showed that the vast majority (80%) of the participants could be considered prosocial rather than egoistic when considering resource distribution in the placebo condition. Two repeated-measures t-tests showed that neither prosocial nor egoistic responses changed across experimental sessions (respectively: $t_{19)} = -1.38$, $p = 0.138$; $t_{(19)} = 0.99$, $p = 0.337$).

Social Reward Questionnaire

The SRQ (Foulkes et al., 2014) has six subscales: Admiration; Negative social potency; Passivity; Prosocial interactions; Sexual relationships; Sociability. A repeated-measures t-test was carried out for each subscale separately, to test for changes across experimental session. Only the prosocial interactions subscale showed a statistically significant change, such that there was an increase in score during the MDMA session compared to placebo session ($t_{(19)} = -3.19$, Bonferroni-corrected for the six subscales $p = 0.03$).

Given this change in the SRQ's prosociality measure, I next carried out two post-hoc regression analyses to examine if the variance in the change in this measure could explain either the change in rejection rates in the UG or the change in cooperation rates in the PD. There was a significant relationship between the change in SRQ prosociality subscale and rejection of unfair FP UG offers, but not with the change in cooperation rates with trustworthy PD

opponents (respectively: beta = -0.51, R^2 = 0.26, p = 0.025; beta = 0.313, R^2 = 0.10, p = 0.191; p-values uncorrected).

4.4.5 Discussion

This study presents a detailed and wide-ranging exploration of the role of serotonin (5-HT) in social cognition, using the serotonergic compound 3,4-methylenedioxy-methamphetamine (MDMA). We investigated the effect of this drug on behaviour in two well-known social decision-making tasks, the Ultimatum Game and Prisoner's Dilemma, as well as on facial affect recognition and empathy. There were clear effects of MDMA on social decision-making. In the UG, there was reduced rejection of unfair offers when acting as the responder in the social conditions (first person and third party), but not the non-social condition (game server). There was also an increase in offer value when acting as the proposer. When responding to offers in the first person condition, there was greater activation in response to fair offers than unfair offers in the superior temporal gyrus (STG) across treatment sessions. In the PD, the effect of MDMA was to increase cooperation with trustworthy opponents but not untrustworthy opponents or the game server. This was accompanied, when receiving feedback of the trustworthy players' decisions, by increased activation in social cognition regions during the MDMA session. These included the posterior superior temporal sulcus (pSTS), mid-cingulate cortex and the supplementary motor area (SMA), as well as the posterior insula/opercular cortex and inferior frontal gyrus (IFG). In the other tasks MDMA reduced recognition of negative facial affect, but had no effect on either cognitive or

affective empathy. MDMA increased scores on the prosociality subscale of the Social Reward Questionnaire (Foulkes et al., 2014), but had no effect on the Social Value Orientation questionnaire (Van Lange, 1999).

The following discussion will be formed of a number of parts. First I will discuss the social decision-making results; the Prisoner's Dilemma (PD) followed by the Ultimatum Game (UG). I will then discuss the tasks for which we did not obtain neuroimaging data, the Affective Bias task and the Multifaceted Empathy Test (MET). The questionnaires will be referred to in the context of the other tasks. The discussion will end with a final consideration of the pharmacological mechanisms underlying the findings reported in this chapter, building on those discussed in the other sections.

4.4.5.1 The Prisoner's Dilemma

Discussion of Prisoner's Dilemma behaviour

In both single-shot and finitely-repeated games, mutual defection is the game theoretic, 'rational' outcome in the PD (Andreoni and Miller, 1993; Axelrod and Hamilton, 1981; Colman, 2003; Cooper et al., 1996). Despite this, a meta-analysis of over 30 years of research found that studies most frequently reported 30-40% cooperation rates (Sally, 1995). High cooperation rates have continued to be seen in recent PD research (e.g. McClure et al., 2007; Rilling et al., 2002; Wood et al., 2006). This was also seen in the current analysis, with participants' cooperation rates centred around approximately 40% even when they were playing with an untrustworthy opponent. At its core, this appears to

suggest that the social norm is to cooperate with other people to obtain mutually beneficial outcomes.

Higher cooperation rates with trustworthy opponents than with untrustworthy opponents were paralleled by differences in average trust rating for each opponent type. Indeed, the finding that there was a statistically significant relationship between round-by-round trust ratings and decisions showed that one of the potential mechanisms underlying peoples' decisions on whether or not to cooperate is how much they trusted their opponent at that particular moment. While this may appear obvious, to my knowledge it is the first time this has been directly tested in the PD. As shown by the regression analysis at the end of Section 4.4.4.3, this relationship was not affected by the administration of MDMA; neither were the mean trust ratings of each opponent. This was counter to what was hypothesised and suggests that MDMA did not alter participants' concept of what constitutes trustworthy behaviour, while altering cooperation rates. As reported in Section 4.3.4.2, the mean trust ratings had high test-retest reliability (ICC range across opponent types: 0.76 – 0.96). As such, non-MDMA-related between-session variability should have been low, maximising the power to detect an effect if it was present, sample-size notwithstanding. With this is mind, it suggests that any change in cooperative behaviour was not due to an MDMA-based disruption of the conceptualisation of trustworthiness, but must be due to some other mechanism.

Also counter to our hypothesis, MDMA increased cooperation only when playing with trustworthy players. Had the amount of cooperation increased with both trustworthy and untrustworthy opponents, it would have been interpretable as

MDMA causing participants to cooperate more regardless of the other player's behaviour. Instead, it appears that the MDMA effect is more nuanced, and context-specific. When the other player showed an overall lack of cooperation, participants behaved similar on the drug and placebo, protecting themselves against being taken advantage of by the opponent. When playing mostly cooperative players, however, it appears that following an opponent's compete decision, there was quicker and greater recovery of cooperation in the MDMA session, leading to an overall greater cooperation rate. This is visualised in Figure 4-17D, with the shallower slope for the MDMA session than placebo session in the trustworthy condition. It is likely that this 'recovery' of cooperation is the trust-independent mechanism underlying the differences seen in overall cooperation across treatment sessions.

It is important to refer to the test-retest reliability of the PD decisions reported in Section 4.3.4.2. This aspect of the PD showed poor reliability (range of repeatability estimates across opponents: 0.26 – 0.48). Two considerations can be taken from this. First, for an effect to have been detected for the trustworthy opponent there must have been a consistent effect. Second, the variance in the proportion of cooperative decisions with the untrustworthy opponent was large. As such, if the MDMA effect in this condition was subtle, the low test-retest reliability would have reduced the sensitivity to find it.

Discussion of Prisoner's Dilemma fMRI results

For each period of the task (decision, feedback, trust rating), no differences in brain activity during the placebo session were found when compared across opponent types. When examining the PD imaging literature, one finds that most

studies do not report simple task effects at decision or feedback stages of the task. Rather, comparisons between treatment and placebo or between different types of outcome are reported (cooperate-cooperate vs cooperate-defect, for example) (e.g. Chen et al., 2017; Feng et al., 2015; Rilling et al., 2002; Sun et al., 2016). In an exception to this, Lambert et al reported neuroimaging results for the decision period of repeated, single-shot games (Lambert et al., 2017). The equivalent in the current study would be to compare the first round of each game across opponent types; a comparison we did not have sufficient statistical power to carry out. Those authors reported activity in the cingulate cortex, insula, inferior frontal gyrus and precuneus during the decision phase.

It is perhaps unsurprising to not find simple differences in the main task effects for the decision period across opponent types, as any differences are more likely represented through incorporation of previous rounds' responses over the course of the game. Such differences would be better detected using computational models. The same could be true for the trust rating period. More surprising is the lack of differences in the feedback period. However, as mentioned above, most other studies compare outcome types. The analysis presented here will have incorporated a range of different types of feedback in each condition, thus increasing the variance of signal within each factor in the analysis. Comparing across experimental session is able to detect the effect of treatment regardless of this within factor variance.

The analysis across experimental sessions identified MDMA-induced differences in brain activity when receiving feedback during games with trustworthy opponents. This suggests that the behavioural differences described

above may be due to differences processing social feedback, and how this feedback is integrated in subsequent behaviour. These differences may underlie the recovery of cooperative behaviour described in the preceding section. The broad network of areas found in this contrast have been strongly implicated in social cognition (Adolphs, 2003; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009). While discussing these findings in light of the existing literature, I will argue that the neuroimaging data obtained in the current study represent a greater social engagement with the other players, which in the trustworthy condition led to increased cooperative behaviour.

The pSTS is frequently implicated in theory of mind (ToM) and attribution of intention to others (Deen et al., 2015; Kestemont et al., 2015; Schurz et al., 2014; Van Overwalle, 2009). As described in 0, ToM is the ability to infer the thoughts and intentions of another agent (Baron-Cohen et al., 1985). That changes in behaviour in the PD could be driven by ToM processes is feasible. Indeed, a number of studies specifically looking at interpersonal interactions have highlighted the role of the pSTS in strategic games using computational modelling techniques (Bault et al., 2015a; Hampton et al., 2008; Haruno and Kawato, 2009). Hampton et al (2008) had participants play a strategic game in which they were awarded money based on the combinations of their own and an interacting partner's decisions, not unlike the PD. Using a computational model they found that a region of the STS slightly more posterior to that reported here was involved in processing the influence of one's own strategy on the behaviour of their partner. Crucially, this occurred during the feedback stage of the task. Haruno and Kawato (2009) used a reinforcement learning model to

provide evidence that during the PD, a region of the pSTS, slightly deeper in the sulcus than that reported here, was involved in predicting the partner's strategy during one's own decision phase. It is important to note however that in this study, participants were not led to believe they were playing human partners.

Bault et al (2015) tested a computational model which attempted to explain the development of 'social tie' over the course of a two-player public goods game. They claim that this represents the history of the interaction over multiple rounds, in the form of reactions to the other's behaviour. They found that this was encoded in a region of the right pSTS slightly lateral to that reported in the current analysis. Furthermore, they modelled an 'impulse' factor, which represented the impact of the other player's choice on the participant's own behaviour, and informed the development of the social tie. Their analysis suggested that this impulse factor was also encoded in the pSTS during the feedback period of the task.

To summarise, the studies outlined above provide strong evidence that ToM processing in the pSTS can involve complex computations of both self and other during interpersonal interactions. Any of the processes described above could be expected to be taking place in the iterated PD reported here. The findings in the present study could extend these by suggesting a serotonergic effect underlying these processes. For example, if MDMA were to alter the processing of the impact of the other player's choice during feedback, leading to a differential encoding of the connection, or 'social tie', with the other player (Bault et al., 2015a), this could influence the recovery of cooperation. Furthermore, a greater engagement with how one's own strategy will influence

the other player's strategy (Hampton et al., 2008) could also underlie the changes seen in the behavioural data presented here. While this hypothesis would need to be tested explicitly, with a task designed to enable computational modelling, it points to the possibility that the effects of MDMA on ToM processing in the pSTS act to increase social engagement in the task and with the other player.

Two clusters encompassing bilateral posterior insula/central opercular cortex were also found in the current analysis to be more active when receiving feedback from trustworthy players in the MDMA session compared to placebo session. A large activation likelihood estimation meta-analysis of neuroimaging studies investigating functional parcellation of the insula cortex highlighted a posterior region as being activated in studies utilising empathy tasks (Kurth et al., 2010). This emphasises that although this area is typically known to be largely involved with interoception (Craig, 2002; Kurth et al., 2010), there is evidence of its involvement in other processes, including socio-cognitive processes. Indeed, a study investigating the role of perspective-taking and cognitive appraisal in empathy found involvement of this region (Lamm et al., 2007). I will provide further evidence of this region being in involved in cognitive appraisal below, and hypothesise a role for this in the current findings.

Two non-social reward studies implicate these posterior insula/opercular regions in tasks which could be relevant to the current study. Tanaka et al (2004) provided evidence that this region was involved in a reinforcement learning paradigm in which participants completed a task where accepting immediate losses could lead to longer term gains. The authors claimed a role

for the posterior insula/opercular region in reward prediction at different time scales. Wittmann et al (2007) also found strong activations of bilateral posterior insula/opercular regions in a delay discounting task when participants chose a delayed reward rather than immediate reward. These authors claim that posterior insula is key part of a decision-making network. It must be acknowledged that the paradigms employed by these studies are very different from the PD, but they do act to illustrate a possible role of this region in decision-making.

Further studies have implicated the posterior insula/opercular regions in social decision-making during the UG. Güroğlu et al (Güroğlu et al., 2010; Kirk et al., 2011b) highlighted activation of this region when accepting, rather than rejecting, unfair offers in the UG. Kirk et al (Güroğlu et al., 2010; Kirk et al., 2011b) found that experienced meditators, who accepted more unfair offers than controls, showed increased posterior insula activation in response to unfair offers than controls. Furthermore, Kirk et al (2016) found that mindfulness training resulted in decreased rejection rates, as well as increased connectivity between the posterior insula/opercular region and a septal seed region. The authors discuss this in light of evidence that suggests this seed region is implicated in prosocial behaviours.

Wright et al (2011) altered the context of objectively moderate unequal offers (30%) in the UG by including them in groups of offers which differed by the size of the other offers in the group. 30% offers could therefore be ‘fair’ in the context of the other offers predominantly being lower, or ‘unfair’ in the context of the other offers predominantly being higher. They claimed that objective inequality

and social context were integrated in the posterior insula/opercular region. Finally, Grecucci et al (2013) carried out a UG study in which participants were trained in emotional reappraisal of the intentionality of unfair offers. They found that such reappraisal strategies not only altered rejection rates, but that activity in the posterior insula/opercular region was modulated by these regulation strategies. These authors suggested that differential processing of visceral interoceptive representations could be a mechanism by which the reappraisal strategies affected the emotional perception of the other players' behaviour. Indeed, a dual fMRI meta-analysis/lesion study approach has recently argued that the insula cortex and its networks play a role of integrating bodily signals for the emergence of social and affective behaviours (Adolfi et al., 2017).

In summary, the studies discussed in the preceding paragraphs paint a possible picture of a nuanced role of the posterior insula/opercula region in changes to social decision-making seen in the current study. All of the UG studies outlined above have in common alterations to behaviour in response to norm violations, and concurrent changes in activation of this region. The same is true for the current study – a quicker and greater recovery of cooperative behaviour following norm violations by trustworthy opponents. Speculatively, reappraisal of the social context in which these violations occur (i.e. an acknowledgment that the opponent is mostly trustworthy) may underlie the changes seen in behaviour. To test this we would have needed to have an explicit fixed questionnaire or interview after the tasks that attempted to delve further into the motivations underlying participants' behaviour in the tasks.

There are of course other possible, non-task-related interpretations of MDMA-induced activity in an area involved with interoception (Craig, 2002; Kurth et al., 2010). MDMA is known to affect the sympathetic nervous system, as well as increase blood pressure, heart rate and peripheral body temperature (Clark et al., 2014; Liechti et al., 2000; Mithoefer et al., 2011). Any of these could feasibly alter interoception, and therefore lead to changes in the posterior insula/opercular region. However, this does not explain why such changes were not seen across opponent types when comparing the MDMA session to the placebo session. Indeed, why *any* of the changes in neural activity were not seen across opponent types is an interesting question, and will be addressed later in this discussion.

The cingulate cortex is frequently implicated in social cognition (Apps et al., 2016; Bernhardt and Singer, 2012; Fan et al., 2011; Gabay et al., 2014; Rushworth et al., 2013). It has been argued that the anterior cingulate cortex (ACC) and anterior parts of the mid-cingulate cortex (aMCC) are involved in processing values and outcomes, and how these outcomes influence subsequent behaviour (Behrens et al., 2008; Kolling et al., 2016). Furthermore, recent research has attempted to differentiate between the role of cingulate gyrus and cingulate sulcus, and argues that while both are involved in reinforcement learning, the cingulate *gyrus* tracks the motivation of others during interactive tasks (Apps et al., 2013; Apps et al., 2016; Lockwood, 2016).

In the results presented in the current study, the change in cingulate activation spanned both the mid-cingulate gyrus and mid-cingulate sulcus. The analysis presented here does not enable a nuanced assessment of the contribution

made by the change in activity in the mid-cingulate to the decision-making process. By producing a reinforcement learning model of the task, it may be possible to disentangle the relative contributions of areas within this cluster, but this is beyond the scope of the current analysis.

The research described above highlights cingulate areas more anterior to those see here, although some are only marginally so. The changes in activation seen in the current study are in a region which has been proposed to make up part of a cingulate motor area (Beckmann et al., 2009; Liberg et al., 2014; Wadsworth et al., 2017). To my knowledge, this is the first time this region of the cingulate cortex has been implicated in social decision-making. It is possible that when receiving feedback of the other player's decision, the participant immediately begins to consider their next decision. As such, response to the feedback and action planning could both be represented in the changes in activation captured in this contrast.

A recent, comprehensive review of studies investigating the MCC, incorporating functional imaging, cytoarchitectural and histological studies, argues for a functional delimitation into anterior and posterior MCC regions (aMCC and pMCC, respectively; Vogt, 2016). The cluster reported here spans this boundary. Vogt argues that aMCC is highly innervated with dopamine DA1 receptors and plays a role in action selection based on the rewarding or aversive properties of the action. Furthermore, the review makes the case that this region plays a key role in feedback-mediated decision-making. The case is made that pMCC is involved in rapid, reflexive action. In the current study, this latter explanation does not easily sit with the finding of pMCC during the

feedback period of the PD. Speculatively, the MCC changes could represent alterations to the incorporation of feedback into the planning of the next decision, and its associated action.

To conclude this section I will briefly summarise the discussion of the PD data thus far. Prior to discussing the fMRI findings of the Prisoner's Dilemma, I speculated that the increased cooperation seen with the trustworthy player during the MDMA session compared to placebo session was due to a quicker and greater recovery of cooperation following a compete decision by the other player. In the preceding paragraphs I have argued that the neuroimaging results potentially support an interpretation that this is due to greater social engagement with the task and other player. I have argued that ToM regions may differentially regulate the social connection with the other player, including how one's own actions will affect those of the other. This could influence or be influenced by different activation of the posterior insula/opercular regions which may inform the reappraisal of the other player's intentionality and their effect on the player's own emotional response to their behaviour.

The difference between trustworthy and untrustworthy opponents

It is interesting that MDMA-related changes were only seen when playing the PD with trustworthy players. This behavioural finding was supported by the equivalent finding in the neuroimaging results, and suggests that participants did not differ in their ability to recognise untrustworthy players. Indeed, this is supported by the fact that trust ratings did not change across experimental sessions. The design of the task was such that untrustworthy players always competed for the first two or three rounds of the game. Perhaps these opening

decisions are enough for the player to establish that the other player is unlikely to be persuaded into cooperating, and this process is unaffected by the mechanisms underlying the effect of MDMA. Future research would do well to investigate this further, by having untrustworthy opponents cooperate at the beginning of the game. Perhaps this change would introduce enough uncertainty that the MDMA effect would lead to greater cooperation rates.

It is important to note that there was large variation in how participants responded to untrustworthy players in both treatment sessions (see Figure 4-17). This variation may be hiding distinct strategic groups in the sample, with some who did in fact cooperate more in the untrustworthy condition during the MDMA session. If this were the case, the improved power provided by increased sample size, or by increasing the number of opponents each participant faces, would allow an analysis of the fMRI data which could attempt to clarify differences in processing of these different groups. The data is currently being analysed further to establish if a reinforcement learning model can be applied to the data to tease apart such differences in strategy. If so, parameters from this model could be included in the fMRI analysis to potentially reduce the unexplained variance in the BOLD signal, thus improving the sensitivity to detect an MDMA effect in the untrustworthy condition if there is one.

4.4.5.2 The Ultimatum Game

Discussion of Ultimatum Game behaviour

In the placebo session, participants' Ultimatum Game (UG) behaviour conformed to that which was expected; namely, that there would be greater rejection of unfair offers in the first person (FP) and third party (TP) conditions than in the game server (GS) condition. Furthermore, that there would be greater rejection of unfair offers than fair and hyper-fair offers.

With regard to the effect of MDMA on this behaviour, our hypotheses were only partially supported. There was a lower probability of rejecting an unfair offer in the social conditions (FP and TP) during the MDMA session than the placebo session. However, there was no difference in the MDMA effect between the social conditions – we had hypothesised that MDMA would not alter TP rejection rates.

The results of the current study extend those of other studies which have investigated the serotonergic underpinnings of UG behaviour (Crockett et al., 2008; M. J. Crockett et al., 2010, 2013). These studies manipulated serotonin levels with the administration of SSRIs and acute tryptophan depletion, and found, respectively, decreased and increased rejection of 30% offers. Rejection of more extreme unfair offers (10-20%) remained unchanged. The current findings, of reduced rejection rates across all unfair offers, establish that those studies may have been limited by the potency of the serotonergic manipulations employed, but supports their overall findings.

In the UG, rejection behaviour is often considered altruistic punishment – the costly punishment of an other's violation of social norms – and is a well-replicated finding (Civai et al., 2013; Fehr and Fischbacher, 2004b; Gabay et al., 2014; Güth et al., 1982; Sanfey, 2003). The modulation of UG behaviour by serotonergic manipulation has been discussed by Crockett et al. (2013) as being indicative of serotonin's role in impulsive choice and reactive aggression, and they suggest that a reduction in rejection rates of unfair offers with increased serotonin is due to harm aversion brought on by greater deliberation (i.e. less impulsive choices) (Crockett, 2009; Crockett et al., 2013; Crockett et al., 2010). When discussing a different series of studies, Civai et al (Civai et al., 2010a; Civai, 2013b; Civai et al., 2013, 2015) argues against the idea that rejection behaviour is solely due to negative emotional reaction to unfairness. They claim that the finding that people reject unfair offers in TP conditions (as seen in the present study), when they are not affected by the outcome, is evidence of inequality aversion over and above reactive negative emotion.

In order to interpret the results from the present study, it is important to first point out that reduction in rejection rates was not due to a change in reward sensitivity. The design of the version of the UG used in this study included a range of stake sizes, such that unfair offers could range from an absolute value of £1.00 to £9.50. As such, if participants were to become either more or less sensitive to monetary reward, it is possible this would be reflected by a differential change in rejection at different levels of absolute value. This was not the case. Furthermore, we explicitly tested for reward sensitivity in a reaction time task after the scanning session, and this too did not suggest participants

had a greater desire for monetary reward during the MDMA session. Furthermore, the variance in changes in reward sensitivity did not explain the variance in change in rejection rates in the FP condition. As such, the reduction in rejection rates seen in the FP condition cannot be interpreted simply as an increased sensitivity to monetary payoff. While one must be cautious when interpreting null results, this is further supported by the finding that when participants made offers to other players, their percentage offer *increased* during the MDMA session compared to the placebo session.

One possible interpretation of these results is that participants were willing to accept lower offers due to higher loss aversion during the MDMA session. Crocket et al (2015) specifically included a loss aversion parameter in a computational model of 'moral' decision-making, and found that increasing serotonin with SSRI treatment did not change this. Murphy et al (2009) carried out an experiment which used tryptophan supplements to increase serotonin availability during a paradigm designed to investigate decision-making under uncertainty. The authors reported a *reduction* in loss aversion with increased serotonin. In a pharmacological study, Macoveanu et al (2013) found that blockade of the 5-HT2A receptor with ketanserin, made participants more risk-averse. Risk aversion has been highly correlated to loss aversion, albeit with a much more economics-focused viewpoint (Goldstein et al., 2008). Finally, a review of the literature looking at monoamine influence on risk in decision-making concluded that serotoninergic neurotransmission may ease loss aversion rather than increase it (Takahashi, 2012). Taken together, the

evidence suggests an MDMA-induced increase in personal loss-aversion is unlikely to account for the reduction in rejection rates seen in the current study.

The finding that FP and TP rejection rates both decreased during the MDMA session could suggest that there was an overall decrease in equality considerations. Such an interpretation would support Civai's (2013) interpretation that rejection behaviour in the UG goes beyond emotion reactivity and takes into account fairness preferences and inequality aversion. However, the finding that the vast majority of participants scored as 'prosocial' in the social value orientation questionnaire (SVO; Van Lange, 1999) in the placebo session, and that this did not change in the MDMA session, suggests that there was no reduction in overall fairness preferences. Again, one must be cautious interpreting null results, although the finding of an increase in the prosocial subscale of the Social Reward Questionnaire (SRQ; Foulkes et al., 2014) does not support an interpretation that participants cared less for equality and fairness. This subscale includes the following questions, amongst others:

i) I enjoy treating others fairly;

ii) I enjoy making someone feel happy;

iii) I enjoy feeling emotionally connected to others.

Not only does this directly reference fairness considerations, these speak to the sense that the effect of MDMA increased the feeling of connectedness to other people. When discussing behaviour in the tasks at the end of each session, participants often said, during the MDMA session, such statements as: "It didn't seem fair to deprive the other person of any money"; "I didn't know his situation – maybe he needed the money more than I did." In light of these qualitative

statements, the harm aversion model of serotonergic influence on the UG appears to be supported by the present study, albeit tentatively. Taking into account the finding that the individual increases in the prosociality measure on the SRQ predicted the magnitude of the decrease in rejection rates in the FP condition, I would argue that in the case of MDMA administration, this harm aversion was facilitated by an increased concern for the direct relationship with the other players, and that this concern was more motivating than fairness and equality considerations. The inclusion of an impulsive choice task, such as that used by Crockett et al (2010), would have enabled us to establish if decreased rejection behaviour was mirrored by a decrease in impulsive choice behaviour. If not, it would provide stronger evidence for the argument given above.

It should be noted that the previous paragraph does not speak against Civai's (2013) interpretation of the concepts underlying rejection behaviour under normal conditions. Indeed, if TP unfair offers do not cause direct emotional arousal, as suggested by Civai et al (2010; 2012), the fact that there was a decrease in rejection in both conditions still supports the argument that rejection behaviour is due to more than mere emotional reactivity. Indeed, the current findings possibly extend this to suggest that serotonergic modulation of UG behaviour by MDMA also moves beyond a change in emotional reactivity to being treated unfairly.

Ultimatum Game fMRI results

The fMRI analysis of the UG did not confirm any of our hypotheses. One analysis, which was restricted to the FP condition, found a main effect of fairness across treatment sessions, such that there was a higher activation of

posterior superior temporal gyrus (pSTG) in response to fair, compared to unfair.

As outlined in the meta-analysis reported in 0 (Gabay et al., 2014), there are robust findings of anterior insula, ACC, SMA, mPFC, putamen and cerebellar activations in neuroimaging studies of the UG. The lack of findings when comparing unfair to fair offers in the placebo condition in the current analysis is particularly surprising given the fact that the task design was very close to those studies included in the meta-analysis. Furthermore, there were clear behavioural changes across conditions. In order to explore the data and effect of task, a number of analyses were carried out.

First, the effect of responding in the placebo condition was analysed. This tested for activations at the time of selecting the response, regardless of whether it was to accept or reject, across all conditions during the placebo session. Very large clusters incorporating occipital, cerebellar and motor areas provide a sanity-check that the task is showing some neural activity due to responding to the task. Next, all assumptions were removed from the expected shape of the neural response to the task, by defining a finite response impulse (FIR) model. This model revealed some changes in activity of three clusters as the trial progressed. However, the timing of these changes (decreases in activity 14 seconds after the beginning of the trial) does not seem to relate to task stimuli.

The finding of pSTG activation for fair versus unfair offers is a reasonable finding, but it is difficult to trust given the lack of other results in the presence of clear behavioural differences across conditions and experimental sessions.

Behaviourally, the task was validated with a test-retest reliability study and was based on similar tasks in the literature. Furthermore, one could argue, it was better controlled than many of the tasks in the literature, given the control for stake sizes. One possible explanation for the lack of neural results is the frequency with which offers were presented – approximately one every ten seconds. This could mean that the neural responses are correlated across conditions, although the conditions were randomised in an event-related design, which should have protected against this possibility.

Greater exploration of this task design will be required in order to refine it for future studies (see Appendix F for some of these). Systematically varying different aspects of the timing will hopefully produce a task that is able capture the neural responses to unfairness. By establishing the neural correlates of the behavioural changes seen with MDMA, it will hopefully be possible to further elucidate the cognitive mechanisms underlying these changes.

4.4.5.3 Affective bias

In this study we have replicated the finding that MDMA reduces accuracy in identifying negative facial expressions (Bedi et al., 2010; Hysek et al., 2012, 2013; Matthew G Kirkpatrick et al., 2014; Schmid et al., 2014). The results in the literature are mixed, however. Two of these studies reported reduced anger and fear recognition, as seen in the present study (Hysek et al., 2013; Matthew G Kirkpatrick et al., 2014). Bedi et al (2010), however, only found a reduction in the recognition of fearful expressions. Furthermore, Schmid et al (2014) only

saw reductions in recognition of sad expressions. Hysek et al (2012) reported *improvements* in positive affect recognition.

On balance, the literature appears to support the decrease in negative affect recognition following administration of MDMA. Interestingly, the effects of other serotonergic manipulations are far less clear-cut. In a review of the literature Merens et al (2007) reported on studies that found both increases and decreases in fear, anger and happiness recognition, across a variety of different methods, including ATD and acute SSRI treatment. The studies reviewed, however, did have a large variation in the demographic characteristics of their samples.

MDMA has been shown to increase plasma oxytocin levels (e.g. Kamilar-Britt and Bedi, 2015; Kirkpatrick et al., 2014; Kuypers et al., 2014; Wolff, 2005). One possible reason for the apparent consistency of MDMA effects on emotion recognition compared to other serotonergic manipulations could be that it is mediated in part by this oxytocin effect. However, a small meta-analysis of oxytocin effects on facial affect recognition found an overall improvement in recognition across both negative and positive emotions (Shahrestani et al., 2013). This is at odds with the results of the present study.

The effects seen in this study do not match the effects seen with SSRIs or oxytocin, both components of MDMA mechanisms. MDMA also acts on the dopamine (DA) and noradrenaline (NA) neurotransmitter systems (de la Torre et al., 2004; Green et al., 2003). As discussed below in Section 4.4.5.5, there is limited evidence that pharmacological manipulation of these systems, particularly the NA system, may alter emotion processing including facial affect

recognition. It is not possible to parse the relative contribution of the different MDMA-modulated mechanisms with the data presented here. We did collect plasma oxytocin samples and analysis of this data will help to inform the interpretation of these findings.

4.4.5.4 Multifaceted Empathy Test

The current study did not replicate previous findings with regard changes in empathic processing with MDMA administration. A pooled analysis of six studies investigating the effect of MDMA on the MET has recently been published (Kuypers et al., 2017). This analysis found that MDMA increased both explicit and implicit affective empathy. The version of the MET used in the current study tested only explicit affective empathy, and no changes were found across experimental sessions.

This task was conducted near the end of the period in which participants felt subjective effects, but a lack of sensitivity based on the timing of the test does not explain the difference with other studies because this task was always conducted just prior to the Affective Bias task which demonstrated alterations in negative affect recognition. Furthermore, the timing of completing this task was comparable to the studies discussed above.

Looking at the details of the other studies finding MDMA-mediated differences in empathy, the effects of treatment on affective empathy appear subtle. For example, looking at Table 2 of Kuypers et al (p. 594; 2017), the mean of the differences between MDMA and placebo sessions for positive valence, affective

stimuli across the six studies is 0.52. The rating scale in the task is out of nine. The current study found a comparable mean difference of 0.46 for positive valence images. It is possible the sample size of the current study did not provide sufficient power to detect this size of effect. The sample sizes of the studies included in the pooled analysis ranged between 16 and 30. Also worth considering are the scores themselves. Again taking positive valence, explicit affective empathy as an example, the studies included in the analysis by Kuypers et al reported mean scores ranging from 4.23 to 5.61 in the MDMA session. The current study found a mean score of 5.57 in the *placebo* session. Across the range of outcome measures, the sample in the current study scored higher in the placebo session than most samples during the MDMA session in the pooled analysis reported by Kuypers et al. Therefore, the possibility exists that the sample tested in the current study had particularly high baseline empathic responses, and as such were less likely to have a discernible increase following MDMA administration.

Also worth noting is the slightly different version of the MET used in the current study to that used in those discussed above. The current study used a short form of the task circulated by the researchers who designed the original. To my knowledge no validation of the newer version has yet been published, although a personal communication stated it had been validated internally (Dziobek, personal communication).

4.4.5.5 Pharmacological mechanisms underlying the effect of MDMA

MDMA pharmacology is complex. It acts to increase the synaptic availability of serotonin through the reversal of the 5-HT transporters, as well as acting as a direct agonist at the 5-HT2A receptor. In addition to this, it increases the availability of dopamine (DA) and noradrenaline (NA; de la Torre et al., 2004; Green et al., 2003). While the magnitude of the 5-HT effect is larger than the DA and NA effects, their role in the MDMA response seen here should not be discounted without appropriate consideration.

Few studies have specifically examined the role of these neurotransmitters in social cognition. The dopaminergic compound d-amphetamine has been shown to have a subtle effect on emotion recognition, such that there was an increase in sensitivity to subtle emotional expressions; this increase was not specific to any emotion (Wardle and de Wit, 2012). Schmid et al (2014) found no effect of the dopaminergic compound methylphenidate on emotion recognition, empathy or 'moral' cognition. In this same study, MDMA produced changes in both emotion recognition and affective empathy.

Some changes in socio-cognitive processing has been seen in studies investigating NA (e.g. Brühl et al., 2011; Harmer et al., 2008). Brühl et al (2011) found fMRI activity changes in response to negative emotional stimuli following administration of reboxetine, a reuptake inhibitor of NA. Harmer et al (2008) found that reboxetine enhanced recognition of disgusted and happy expressions. In the current study it is not possible to differentiate between the NA and 5-HT effects of MDMA on facial affect recognition.

As mentioned above, MDMA has multiple serotonergic effects. As such, it is not possible to draw firm conclusions as to the 5-HT mechanisms underlying the results reported here. However, a recent study has produced a high-resolution atlas of the distribution of different serotonergic receptors in the human brain (Beliveau et al., 2017). Figure 4-20 is a reproduction of Figure 2 from this publication. The highest densities of 5-HT2A receptors are seen in some of the regions found in the PD fMRI data: lateral temporal cortex including the pSTS, and the MCC. Indeed, the density of 5-HT2A receptors in these regions is substantially higher than the other 5-HT receptor subtypes. The density of 5-HT4 receptors also approaches its highest in the lateral temporal lobe; the overlap with the PD imaging findings in this chapter suggests a more direct exploration for the role of these receptors in social cognition, which is currently completely unexplored. Furthermore, areas of highest density of 5-HT transporters include the insula cortex, suggesting high serotonergic innervation of this region. Therefore, the insula activations reported here are potentially the result of increased serotonin release.

Overall, these comparisons do suggest that the PD results reported here are due to MDMA's potent 5-HT activity. One must be cautious when drawing conclusions from this, but given the known receptor mechanisms of MDMA, it does provide tentative evidence that the effects seen in the current study may have a 5-HT2A specific component. Given the studies discussed in previous sections, it is reasonable to postulate similar pharmacological mechanisms underlying the UG.

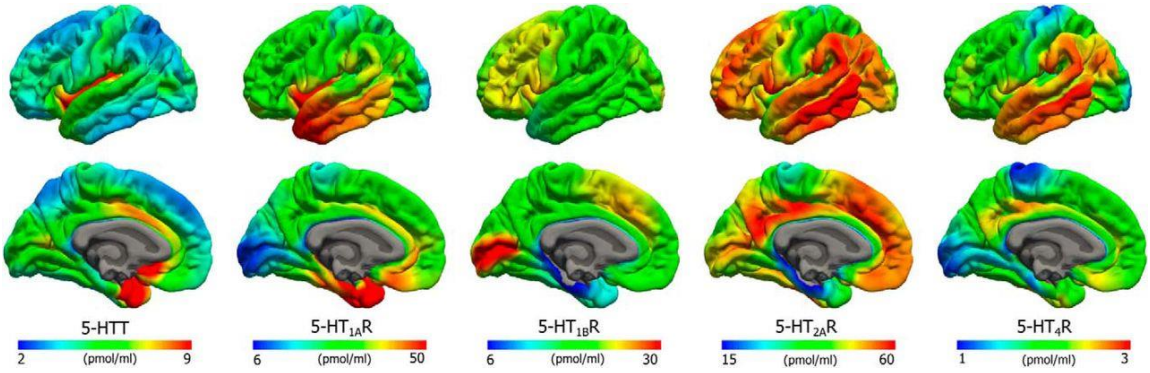


Figure 4-20: reproduced with permission from Beliveau et al (2017): Average density (Bmax) maps for five 5-HT targets on the common FreeSurfer surface (left hemisphere; lateral view, upper and medial view, lower). Color [*sic*] scaling was individually adjusted to highlight features of the distributions.

4.4.5.6 Limitations

A limitation of the current study is the use of an inactive placebo. Given the potent subjective effects of MDMA, participants became aware that they had been given the active compound. This is a recognised challenge amongst researchers investigating compounds with potent subjective effects, and will be discussed in more detail in Chapter 5.

As discussed above, one must be cautious in attributing the MDMA effects seen in this study to changes in serotonergic activity. Better characterisation of the receptor mechanisms could be achieved through 'pharmacological substraction' approaches. For example, a three-arm study could be carried out which included pre-treatment with the 5-HT2A receptor antagonist ketanserin. Alternatively, to establish if MDMA's dopaminergic modulation was an underlying mechanism to the results seen here, one could include a pre-treatment with a dopamine antagonist such as haloperidol.

4.4.5.7 Conclusion

This study has been the first to demonstrate clear effects of MDMA on the social decision-making tasks the Ultimatum Game (UG) and Prisoner's Dilemma (PD). I have argued that underlying the increased cooperation seen with trustworthy players in the PD is a quicker and greater recovery of cooperation following decisions by the opponent to compete, and that this is driven by an increased social connected-ness to the other player. This is possibly driven by reappraisal of negative emotions elicited by norm violations. I have also argued that changes in the UG may be due to an increased harm aversion, again driven by an increased social connection to the other players, whose motivational effect trumps that of fairness considerations, which do not appear to be affected by MDMA. This study also replicated findings that MDMA reduces recognition of fear and anger, while being unable to replicate findings of changes in affective empathy.

Taken together it appears that the serotonergic effect of MDMA causes profound changes in how participants behave during interpersonal interactions. These changes may be context specific, and do not impede the individual from making appropriate judgements when they are being treated 'unfairly' by another agent.

Future work should attempt to elucidate the serotonergic mechanisms by which MDMA has its effect on social decision-making, through the use of other pharmacological agents to either block specific serotonin receptor subtypes, or selective receptor agonists.

Chapter 5 Overall discussion

5.1 Overview of the work reported in this thesis

The aim of this thesis was to present a thorough exploration of the psychopharmacology of specific aspects of social cognition. Deficits of social cognition have been shown to be a key aspect of a number of psychiatric conditions, and has been highlighted as an area requiring greater research in schizophrenia (see 0, Sections 1.3 and 1.4; Baron-Cohen et al., 1985; Collin et al., 2013; Dziobek et al., 2011; Kupferberg et al., 2016; Nuechterlein et al., 2004). Deficits in facial affect recognition and empathy have long been established across psychiatric conditions (e.g. Bora and Pantelis, 2016; Dalili et al., 2015; Dziobek et al., 2011, 2008; Kohler et al., 2010; Lozier et al., 2014; Mazza et al., 2014), and there is also evidence for alterations in social decision-making (see 0, Section 1.5.3; e.g. Csukly et al., 2011; de la Asuncion et al., 2015; Radke et al., 2013; Scheele et al., 2013; Wang et al., 2014; Wischniewski and Brüne, 2011). As such, this thesis has concentrated on these aspects of social cognition: social decision-making, facial affect recognition and empathy.

The work on which this thesis is based began with establishing the need for better treatment options for these deficits, highlighted by the case of facial affect recognition in schizophrenia (see 0, Section 1.4; Gabay et al., 2015). I then carried out a meta-analysis of neuroimaging studies investigating the Ultimatum Game (UG) (see Chapter 2; Gabay et al., 2014). This provided evidence of a network of brain regions underlying UG behaviour and provided a detailed discussion of the hypothesised roles of these regions. Following completion of

this analysis, I carried out two studies employing different serotonergic manipulations to investigate their effect on social cognition. The first, reported in 0, investigated the effect of the psychedelic compound psilocybin on social decision-making and facial affect recognition, and the potential for a src-kinase inhibitor to attenuate these effects. The second, reported in 0, investigated the effect of 3,4-methylenedioxy-methamphetamine (MDMA) on facial affect recognition, empathy, and behaviour in two social decision-making tasks, the UG and Prisoner's Dilemma.

While there was a comprehensive discussion of those studies in their respective chapters, there was no consideration of how each could inform the other. In the following sections I present a discussion of the results in this light. Since the Multifaceted Empathy Test (MET) was only carried out in the MDMA study and has no crossover to the other tasks, these results will not be discussed further below.

5.2 The effect of MDMA and psilocybin on social decision-making

Taken together, the two studies presented in Chapters 3 and 4 confirm the role of serotonin (5-HT) in social decision-making, using two tasks: the Ultimatum Game (UG) and the Prisoner's Dilemma (PD). In the UG, increased 5-HT activity led to greater rejection rates of unfair offers when they were directed both at the self (in both studies) and to a third party (only tested in the MDMA study). The evidence from the psilocybin study suggests that this is likely due to agonism at the 5-HT2A receptor. In the PD, participants cooperated more with trustworthy players, but not untrustworthy players, following administration of

MDMA. This was due to a greater 'recovery' of cooperation following uncooperative decisions by these opponents compared to the placebo session. Since the PD was not completed by the participants in the psilocybin study reported in 0, we cannot conclude that this was due to agonism at the 5-HT2A receptor rather than some other serotonergic effect, although MDMA does act as a direct agonist at this receptor (de la Torre et al., 2004; Green et al., 2003).

In both studies, the central operculum/posterior insula region was implicated. In the MDMA study, this region showed greater activity during the MDMA session compared to the placebo session, when receiving feedback from trustworthy players – the same condition where participants showed greater cooperation. In the psilocybin study, there was greater connectivity of this region to the anterior cingulate gyrus (ACC_g) during the Psilo session compared to the Psilo+ session. In the Psilo+ session, saracatinib appeared to attenuate the psilocybin-induced reduction in rejection rates during the UG. Building on previous research (Grecucci et al., 2013; Güroğlu et al., 2011; Kirk et al., 2011, 2016; Wright et al., 2011), I have argued that this region may have been involved in the reappraisal of the other players' behaviour. In the MDMA-PD task this may have been required for the faster re-emergence of cooperative behaviour. The ACC_g has been strongly implicated in the processing of interacting partners' motivations during decision-making (Apps et al., 2016; Apps and Sallet, 2017; Lockwood, 2016), and the increased connectivity between these regions in the psilocybin study, during the session with lower rejection rates, may support the interpretation that reappraisal of the partners' motivations played a role in the behavioural changes seen.

The finding of increased superior temporal sulcus (STS) activity during feedback from trustworthy players during the MDMA session of the MDMA-PD task also supports the idea that participants incorporate other player's thoughts, beliefs and intentions when playing more cooperatively (Bault et al., 2015b; Hampton et al., 2008; Haruno and Kawato, 2009).

Brain regions and cognitive mechanisms do not function in isolation. Both studies highlighted the involvement of regions implicated in reward processes. In the MDMA-PD task, the anterior mid-cingulate cortex showed greater activity during the MDMA session when receiving feedback from trustworthy players, possibly implicating reward-based action planning. In the psilocybin study, connectivity between the anterior insula (implicated in signalling UG social norm violations; e.g. Civai et al., 2013; Sanfey, 2003) and orbitofrontal cortex (OFC) increased in line with greater rejection rates from the Psilo to Psilo+ session. One could interpret these findings as evidence that not only do other-facing processes underlie social decision-making decisions, but also the integration of these with how rewarding the outcomes are to the self. Indeed, behaviours in social decision-making are often counter intuitive, such that they go against game-theoretic, self-interest-driven predictions (Camerer, 2003; Fehr and Fischbacher, 2004b; Fehr and Gächter, 2002; Güth et al., 1982). As such, for these behaviours to evolve, one could expect the underlying mechanisms to link to reward processing on some level. Indeed, Bhanji and Delgado (2014) argue that while there does not appear to be a specific 'social reward pathway', reward processing plays a role in a number of social processes. The studies presented in this thesis appear to support a role for integrating reward with

social cognitive processes, and that manipulation of the 5-HT system can modulate this.

5.3 The effect of psilocybin and MDMA on facial affect recognition

Both of the studies reported in this thesis had participants complete the Affective Bias task (Bland et al., 2016). This task examines accuracy in identifying four different emotions (happy, sad, anger, fear), and includes a control condition of identifying which age-group faces belong to (child, young adult, middle-aged adult, older adult). No difference was seen across sessions in the psilocybin study. In the MDMA study, there was a reduction in recognition of fearful and angry expressions in the MDMA session.

Taken at face value, these results suggest that serotonergic modulation of facial affect recognition is not achieved through 5-HT2A receptor activity, and that the findings of the MDMA study can be explained through increased activity at other 5-HT receptors. This could be directly tested by investigating the effect of administering the 5-HT2A antagonist ketanserin prior to MDMA to see if this blocked the reduction in fear and anger recognition.

The effect of ketanserin alone on facial processing has been investigated (Hornboll et al., 2013). These authors reported that 5-HT2A blockade altered functional connectivity between the orbitofrontal cortex and amygdala in response to fearful faces. This was not an overt emotion recognition task; rather, participants were asked to judge the gender of the stimulus face. There was no difference in error across sessions, but ketanserin increased reaction times. This does suggest some role of these receptors in facial affect

processing. Kometer et al (2012) also suggested a role for the 2-HT2A receptor when they found evidence that ketanserin attenuated the effect of psilocybin on facial affect recognition reported in that study.

The findings of these two studies counter the lack of an effect in the psilocybin study reported in 0. However, as discussed in that chapter, it could be that the visual disturbances induced by psilocybin disrupted affect recognition in the Kometer et al (2012) study, and not 5-HT2A agonism *per se*. In the study reported in Chapter 3, this would not have been the case because the task was carried out sometime after the most acute effects of the drug had passed. Furthermore, one must be cautious when interpreting the acceptance of the null hypothesis. This study may not have been powered appropriately to detect an effect; specifically the variance in the psilocybin response could have been such that any changes seen were not consistent enough across participants, although effects were seen in the UG performed at about the same time.

5.4 Limitations

As discussed in Chapters 3 and 4, there is recognition in the field of psychedelic research that inert placebos do not sufficiently blind participants to the treatment they receive. One method of addressing this issue would be the introduction of a third arm to the study, administering an active placebo. However, choice of an active placebo is not straight forward for the two compounds under investigation in the studies reported in this thesis.

Psilocybin was administered in an open-label manner for the study reported in Chapter 3. However, if one were to consider using an active placebo-controlled

design, it is difficult to know what would be an appropriate compound to use, as psychedelic drugs have profoundly potent subjective effects. Administration of a very low, but still active dose is one possibility. Another would be to use a compound which acts on a different neurotransmitter system, such as the glutamatergic NMDA receptor antagonist, ketamine, which has dissociative effects. However, the participants recruited in this study had previous experience of psychedelic compounds, so would likely recognise the difference in subjective effects of the two drugs.

An inert placebo was used for the study investigating MDMA. One possibility for an active placebo would be methylphenidate, which produces some mild stimulant effects. These two compounds have been used in comparative studies investigating aspects of social cognition (Hysek et al., 2014; Schmid et al., 2014). Some social effects were seen with methylphenidate, so this would need to be a three-arm study to parse the MDMA effects as compared to inactive placebo. Another possibility for an active placebo in this study would be a lower dose of MDMA. Oehen et al (2013) reported that participants were successfully blinded to a dose of 25mg MDMA compared to 125mg.

Investigation of the dose-response relationship would have been beneficial to both studies reported in this thesis. The benefits of this are two-fold. First, in the absence of true blinding to the active compound, assessment of the dose-response of the cognitive tasks would aid in separating the true effects of the treatment from any placebo effect. Second, use of multiple doses could help establish whether null results are due to particular doses being outside the window of effect for certain cognitive processes.

5.5 Implications and future directions

Whilst the research reported in this thesis is an important step, future studies should improve upon the design of those reported here. By incorporating a dose-response design or employing the use of specific receptor antagonists, the hypothesis that serotonergic mechanisms underlie the changes in behaviour seen here can be tested.

Future studies should continue to establish what underlies social decision-making behaviour in the healthy population. In this thesis I have attempted to highlight the psychopharmacological mechanisms. Equally important are the psychological mechanisms underlying the differences in behaviour across the population. By exploring the reasons behind the differences seen in the general population, one may be able to create a framework for explaining who would respond to pharmacological manipulations.

In Chapter 4 I advanced the hypothesis that a greater 'social tie' was responsible for the recovery of cooperation seen in the Prisoner's Dilemma during the MDMA session. This could be explicitly tested with a small alteration of the task to make it longer and therefore more suitable for fitting a computational model. Doing so would enable one to apply the model used by Bault et al (2015) to the PD in an MDMA study, thus further characterising the social cognitive effects of the compound.

The significance of the research reported in this thesis is the further characterisation of the role of the serotonergic neurotransmitter system in social cognition. This work has suggested that underlying responses to dynamic social

situations are complex mechanisms that are driven by alterations in serotonin receptor activity. Social decision-making is a burgeoning field, and as outlined in 0 is increasingly being investigated in relation to psychiatry. Doing so can help to clarify how higher-level cognitive processes are disrupted in these conditions, and the research presented here further establishes the underlying neural mechanisms in healthy participants.

In Section 1.5.3 of Chapter 1, I reviewed evidence for altered UG behaviour in patients with depression. While there is some heterogeneity in the findings reported, there does appear to be an increase in rejection of unfair offers in these patients. In this thesis I have argued that the reduction in rejection behaviour seen in the two studies may be due to increased aversion to causing harm to a directly interacting partner, motivated by a greater social engagement with that partner. With evidence suggesting that patients with depression show reduced social engagement (Achterberg et al., 2003; Setterfield et al., 2016), the current presentation may provide a cognitive mechanism by which this deficit occurs. None of the reviewed studies showing these differences tested un-medicated patients, but rather patients medicated largely with SSRIs. The results from the current thesis suggest that treatments for depression which more specifically target 5-HT2A receptors as agonists may help to 'normalise' these behaviours in social decision-making, by promoting a greater engagement in social aspects of the tasks.

On the other hand, the evidence reviewed in Chapter 1 suggests that there is a *reduction* in rejection of unfair offers in patients with schizophrenia. This is difficult to interpret in light of the results presented in this thesis, particularly as

the studies finding differences included patients mostly medicated with atypical antipsychotics, which act as antagonists at the 5-HT2A receptor (Seeman, 2004). Schizophrenia is a complex condition, and antipsychotic medication acts on a number of different neurotransmitter systems and receptors (Seeman, 2004), the interactions between which are not fully characterised.

Those studies that found differences in PD behaviour between patients and healthy controls reported reduced cooperation in borderline personality disorder and depression. In light of the current findings, this may be due to changes in the underlying mechanisms incorporating intentionality, appraisal and reward. Again, treatments with specific 5-HT2A agonism may help to 'normalise' behaviour in these tasks. An important finding from the MDMA study is that changes were not seen during interactions with uncooperative partners. If this is borne out through replication, it suggests that treatment in psychiatry has the potential for context-sensitive social cognitive benefits.

The work presented here can be extended in several ways. Computational modelling of complex cognitive processes is a technique which shows growing promise in characterising the nuances of the neural mechanisms underlying them. By applying these modelling techniques in an attempt to characterise psychopharmacological mechanisms, not only could we identify brain networks involved in specific aspects of social decision-making, we could also attempt to establish receptor subtype contributions.

Further psychopharmacological research could attempt to validate the findings here. The use of specific receptor antagonists such as ketanserin would help to establish receptor mechanisms underlying the PD. Indeed, it would also be

interesting to investigate the effect of the src-kinase inhibitor saracatinib on the MDMA effects reported in this thesis.

A number of studies have recently begun to establish the efficacy of compounds such as psilocybin and MDMA as an adjunct to psychotherapy for conditions including depression and post-traumatic stress disorder (e.g. Amoroso and Workman, 2016; Carhart-Harris et al., 2016; Sessa, 2016; Yazar-Klosinski and Mithoefer, 2017). By establishing specific effects of these compounds on the social cognitive mechanisms underlying trust, cooperation and social norm processing, the results presented in this thesis may shed light on the efficacy in the above treatments.

A weakness of the current thesis is that there is no direct neuroimaging comparison across the two studies. Such a comparison would have helped to identify whether there are similar mechanisms underlying changes in task behaviour. Resting state data was acquired during the MDMA study, analysis of which has not been reported here. A collaboration has been initiated to analyse this data, which will enable us to establish how the different serotonergic mechanisms differentially affect network connectivity.

5.6 Overall conclusion

The work presented in this thesis has shown for the first time that MDMA and psilocybin can alter behaviour in social decision-making. Furthermore, it suggests that these changes come about largely through 5-HT2A receptor activity, although this needs to be clarified in the case of the Prisoner's

Dilemma. I have argued that changes in social decision-making come about through greater social engagement with the other players, and that underlying this is altered appraisal of the intentions and motivations of other players. This allows for the context-specific effects seen in the PD, where MDMA altered behaviour with trustworthy, but not untrustworthy opponents. Recruitment, and changes in connectivity, of brain regions involved in theory of mind, cognitive reappraisal and reward processing may be modulated by 5-HT manipulation. This suggests that alterations in this neurotransmitter system, specifically at the 5-HT2A receptor, may underlie differences in how people respond to norm violations and (un)cooperative behaviour in psychiatric conditions.

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Appendix A Methods for Chapter 1, Section 1.4

A literature search was carried out using PubMed and Web of Knowledge databases, entering the search term “schizophrenia AND facial AND emotion AND antipsychotic” in May 2014. In addition, a manual search was carried out of reference sections of papers returned. We included English-language studies that 1) used a task investigating facial emotion processing, 2) specifically investigated the effects of antipsychotic medication, 3) provided pre- and post-medication data and 4) included patients with a diagnosis of schizophrenia. Nine studies met these inclusion criteria, confirmed by two of the authors (ASG and MAM; see Figure 1).

Studies employed a range of tasks, with the predominant outcome measure being number of correct/incorrect responses (*n*=8). The outcome measure from one study (Cabral-Calderin et al., 2010b) was number of phases of facial morphing before a correct response. Where data was not available in an appropriate form, authors were contacted requesting additional information.

For studies investigating multiple antipsychotics, each drug was entered into the meta-analysis separately. These were independent samples. In addition to analysing all antipsychotics together, we also performed subgroup analyses of typical and atypical antipsychotics. Atypical antipsychotics are second generation medications which differ from first generation (typical antipsychotics) in their improved side-effect profile, including reduced extrapyramidal symptoms

(Meltzer, 2004). Hedge's g and its 95% confidence intervals (CI) were calculated for each study and each drug. Hedge's g is a measure of effect size similar to Cohen's d, but corrected for small sample size (Ellis, 2010). A random effects meta-analysis, subgrouped by typical and atypical antipsychotics, was carried out using Review Manager 5.2 (The Nordic Cochrane Centre, 2012), using an inverse variance weighted model. Between-study heterogeneity was assessed using the I^2 statistic. Egger's intercept and visual inspection of funnel plots was used to assess evidence of publication bias (Matthias Egger et al., 1997). We also carried out meta-regression analyses using the metareg module in Stata Statistical Software (Harbord and Higgins, 2008; StataCorp, 2011) to assess the influence of symptoms, age and gender on task performance.

One study (Cabral-Calderin et al., 2010b) reported subscales of tasks with no overall score. The total score and standard deviation (SD) for these subscales were calculated, using an estimation of the correlation coefficient between subscales as 0.8 in order to sum the SDs. Sensitivity analyses were carried out to determine if altering this estimation affected the pooled effect size.

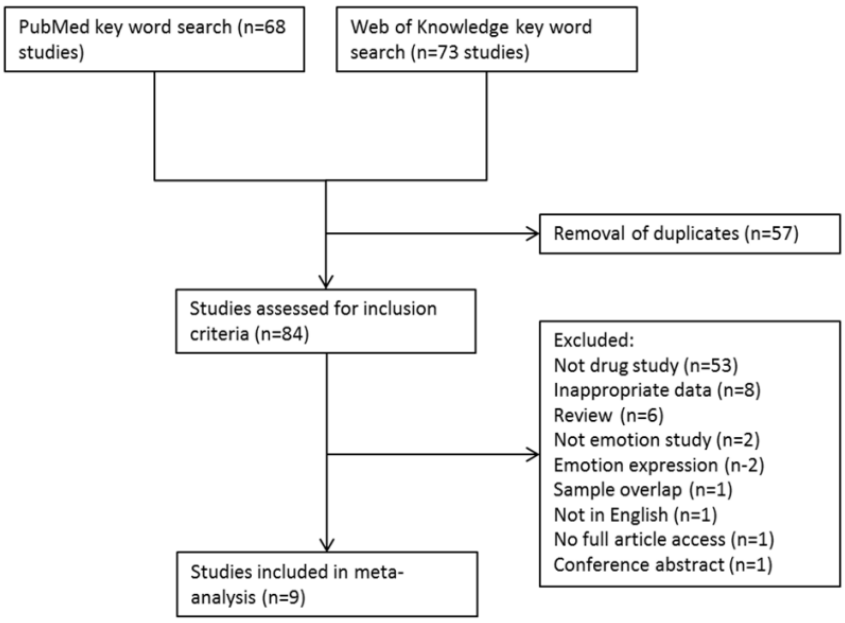

Figure A-1: Flowchart showing study selection for the meta-analysis investigating

Table A-1: Details of studies included in the meta-analysis of antipsychotic treatment effects on facial affect processing in schizophrenia

Study first author	Date	Drug	Dosage mg/day	Study design	N	Sex (% M)	Mean age (+/-we: positive/negative symptom scale)	Symptom severity			Duration of illness (years)	Time from baseline to follow-up (weeks)	Task (R = recognition, D = discrimination)
								Measure	Baseline	Endpoint			
Lewis	1995	Haloperidol	5-20	D, P, FL	18	No data	38.9	BPRS	45.7	40.2	Not given	2	FAR (R)
Wölwer	1996	Haloperidol	531±313	W, P,	12	67	33.2	(Across all	25.72(8.13)	17.61(4.77)	6.7 ± 6.9	4	FAR
		Perazine	436±217 CPZE	FL	20	70	31.8	patients) BPRS (+we) (-we) SANS	10.84(3.14) 13.63(5.00)	9.53(3.42) 11.56(4.52)			(R)
Bediou	2007	Haloperidol	10 (1.6)	P, D, FL	26	92	24.3	(Includes non-completers) PANSS (+we) (-we) PANSS(general)	29.5(7.1) 27.2(7.6) 39(6.6)	10.2(6.7) 11.4(3.8) 20(4)	First episode	4.3 (mean)	EFER (R)
Sergi	2007	Haloperidol	8	P, DB, R, FD	20	100	50	BPRS (+we)	Not given	3.0 (0.9)	Not given	8	FEIT
		Olanzapine	15		40	86	49.2	(-we)		2.1 (0.8)			(R)
		Risperidone	4		40	87	48.2	(+we)		2.5 (1.0)			
								(-we)		2.3 (0.8)			
								(+we)		2.8 (1.0)			
								(-we)		2.3 (0.8)			
Behere	2009	Risperidone	4	P, D, FD	25	70	29.4	SANS SAPS	60.2(25.1) 29.3(13.6)	43.2(13.1) 12.6(12.1)	1.4 (1.5)	5.5 (mean)	TRENDS (R)
Harvey	2006	Quetiapine	529.62	P, DB, R, FL	124	78	40.2	PANSS (+we)	16.77(6.56)	Not given	Not given	8	PEAT
		Risperidone	(288.28) 5.33 (2.13)		142	76	39.9	(-we) (total) (+we) (-we) (total)	17.27(5.95) 22.52(22.10) 17.66(5.54) 18.58(5.62) 71.09(20.76)				(intensity)
Penn	2009	Perphenazine	8	P, R,	159	75	41.0	Across all	74.29(17.48)	Not given	14.49 (10.92)	8	FEDT
		Olanzapine	7.5	DB,	170	(overall)	(overall)	patients					(D)
		Quetiapine	200	FL, W	161			PANSS (total)					
		Risperidone	1.5		161								
Cabral-Calderin	2010	Quetiapine	413.5 (165.6)	P, W, FL	34	56	35	PANSS (+we) (-we) (general) (total)	15.58(7.16) 16.5(7.94) 34.32(12.55) 66.41(22.83)	12.76(5.81) 14.23(7.29) 28.23(10.24) 55.23(18.96)	9.22 (8.54)	12	EEMT (R)
Daros	2014	Risperidone	3.53 (1.8)	P, W, FL	19	79	21.5	PANSS (+we) (-we) (total)	24.74(4.41) 19.26(5.67) 80.11(15.47)	15.61(4.96) 15.61(6.21) 61.61(16.71)	First episode		PEAT (intensity)

P: pre-post design; D: drug-free baseline; R: randomised; W: washout/drug cross-over period; DB: double-blind; FD: fixed-dose; FL: flexible dose; FAR: facial affect recognition (Ekman and Friesen, 1976); EFER: emotional facial expression recognition; FEIT: facial emotion identification test, photos developed by Izard (1971) and Ekman and Friesen (1976); TRENDS: Tool for Recognition of Emotions in Neuropsychiatric Disorders (Behere, 2009); PEAT: Penn Emotional Acuity Test (Comblatt, 1989); FEDT: Face Emotion Discrimination Test (Kerr and Neale, 1993); EEMT: Emotional Expression Multimorph Task (Mendoza, 2011); CPZE: Chlorpromazine equivalents; BPRS: Brief Psychiatric Rating Scale; SANS: Scale for the Assessment for Negative Symptoms; SAPS: Scale for the Assessment for Positive Symptoms; PANSS: Positive and Negative Syndrome Scale.

Results of literature search

After 57 duplicates were removed, 84 studies were returned by the original search. Of these, nine studies met the inclusion criteria, investigating six antipsychotics (haloperidol, perphenazine, perazine, riseridone, quetiapine, olanzapine)(Bediou et al., 2007; Behere et al., 2009; Cabral-Calderin et al., 2010b; Daros et al., 2014; Harvey et al., 2006; S. Lewis and Garver, 1995; Penn et al., 2009; Sergi et al., 2007; Wölwer et al., 1996) in 1152 patients with schizophrenia (see Table 1 for study details). Overall there was no bias with regard to which emotions were examined. Two studies (Daros et al., 2014; Harvey et al., 2006) only focused on two emotions – the range of intensity from very happy to very sad; four studies (Behere et al., 2009; Cabral-Calderin et al., 2010b; S. F. Lewis and Garver, 1995; Wölwer et al., 1996) investigated processing of happiness, disgust, sadness, surprise, anger and fearful expressions; one study (Bediou et al., 2007) investigated processing of neutral, happiness, disgust, fear and anger; two studies investigated processing of happiness, sadness, anger, surprise, fear and shame (Penn et al., 2009; Sergi et al., 2007).

Appendix B Task instructions

Chapter 3 Ultimatum Game instructions (test retest and psilocybin study)

You are going to take part in a two-player game.

In this game, the first player is given £20 and is instructed to split it with the second player. If the second player accepts how the money has been split, then both players receive the amount of money decided by the first player. On the other hand, if the second player rejects the proposed split, neither of them will receive any money at all for that round.

Here is an example: Player one is given £20 to split with player two. Player one offers player two £8. If player two accepts this offer, player two receives the £8 and player one keeps the remaining £12. If player two rejects the offer, the full £20 is taken back from player one and neither player receives any money from that round.

Do you have any questions about the rules of the game?

In a moment you will play this game against other people. You will sometimes be making decisions for yourself, and sometimes your decision will be on behalf of another person.

The other people are from an event we recently held, where a group of people played this game. It was set up so that each player had the opportunity to play the game with every other person, both as player one and player two. For each

interaction, players were asked to make a second offer, intended for the participants in *this* study.

When you play the game, you will sometimes play as player two: you will be presented with an offer taken from this previous event, and you will be asked to accept or reject it. On other trials it will be the same, except you will be responding on behalf of another player. In this case you will see what player one offered player two, and you will be asked to accept or reject that offer on behalf of player two. Sometimes, you will be presented with an offer which has been randomly generated by a computer, and asked whether you want to accept or reject it.

When you have completed the whole study, you will receive a proportion (1%) of the money earned based on the decisions you have made on your own behalf. The players from the group event will also be paid depending on how you and other participants in this study respond to their offers.

All names of the other players have been randomly assigned to protect the anonymity of our research participants.

Chapter 4 instructions (test retest)

In this study you will be logging onto a shared network which we have developed with Imperial College London and University College London. When logged on to this network you will be connected to other participants at one of these sites. They may or may not be involved in a drug study or even an MRI study, but will be participating in research where the researchers are interested in the same social processes as we are. Whenever you connect to another

player you will be given a name for them. All names of the other players have been randomly assigned to protect the anonymity of our research participants.

You will be playing two different types of game with the people you connect with, which I will explain to you now.

Prisoner's Dilemma

In the 'compete or cooperate' game you will connect to another player and play repeated rounds with the same person. On each round you will each, simultaneously be asked to Compete or Cooperate with the other player, and will then be awarded points depending on the combination of your responses. If you both choose to Cooperate, you will receive 90 points each. If you both choose to Compete, you will receive 60 points each. If one of you chooses to Cooperate and the other chooses to Compete, the cooperator will receive 30 points while the competor will receive 120. So it is clear that the best for everyone is to cooperate, but that opens oneself up to being taken advantage of by the other person competing.

You will play between eight and 15 rounds with each player. On each round you will be given three seconds to decide to Compete or Cooperate. You will then be given feedback as to what the other player chose, and how the points will be distributed. You will then be asked to rate your trust in the other player, from one to seven. When rating your trust in the other player, don't necessarily just base it on their most recent decision, but consider all the rounds you've played with that player. You have five seconds to rate your trust, before the next round with that player starts. When you have completed all rounds with that player,

you will see “Your game with XXX has finished”, and the server will then look for another player to connect to.

You will play two ‘runs’ of this game. On each run you will play multiple rounds with three other players. The middle player of each run will in fact be a computer programme which will randomly decide whether to Compete or Cooperate on each round. Its decision will not be affected by your own behaviour. Other than that, the gameplay is exactly the same as when you are connected to other players.

Ultimatum Game

An important thing to remember when playing this game is that you will only interact with each other player once. That means that neither you nor they can learn from the others behaviour. You play one round with one player and are then connected to a different player. In the real world, we can never be sure exactly how many people are logged on to the network at any one time, so it is possible that you will in fact reconnect with a player twice, but you will never know because each time you connect with someone they are assigned a new, random name; so treat each decision as independent.

In this game, the first player is given £20 and is instructed to split it with the second player. If the second player accepts how the money has been split, then both players receive the amount of money decided by the first player. On the other hand, if the second player rejects the proposed split, neither of them will receive any money at all for that round.

Here is an example: Player one is given £20 to split with player two. Player one offers player two £8. If player two accepts this offer, player two receives the £8 and player one keeps the remaining £12. If player two rejects the offer, the full £20 is taken back from player one and neither player receives any money from that round.

When you play the game, you will sometimes play as player two: you will be presented with an offer taken from this previous event, and you will be asked to accept or reject it. On other trials it will be the same, except you will be responding on behalf of another player. In this case you will see what player one offered player two, and you will be asked to accept or reject that offer on behalf of player two. Sometimes, you will be presented with an offer which has been randomly generated by a computer, and asked whether you want to accept or reject it. Sometimes you will also be asked to play as player one, and make an offer to another player.

When you have completed the whole study, you will receive a proportion (1%) of the money earned based on the decisions you have made on your own behalf.

Chapter 4 instructions (MDMA study)

(NOTE: The instructions for the Prisoner's Dilemma remained the same as the test retest instructions above. For the Ultimatum Game, there was a slight change in the task, such that the total stake varied. The below instructions reflect this change.)

An important thing to remember when playing this game is that you will only interact with each other player once. That means that neither you nor they can learn from the others behaviour. You play one round with one player and are then connected to a different player. In the real world, we can never be sure exactly how many people are logged on to the network at any one time, so it is possible that you will in fact reconnect with a player twice, but you will never know because each time you connect with someone they are assigned a new, random name; so treat each decision as independent.

In this game, the first player is given a sum of money and is instructed to split it with the second player. If the second player accepts how the money has been split, then both players receive the amount of money decided by the first player. On the other hand, if the second player rejects the proposed split, neither of them will receive any money at all for that round.

Here is an example: Player one is given £20 to split with player two. Player one offers player two £8. If player two accepts this offer, player two receives the £8 and player one keeps the remaining £12. If player two rejects the offer, the full £20 is taken back from player one and neither player receives any money from that round.

When you play the game, you will sometimes play as player two: you will be presented with an offer taken from this previous event, and you will be asked to accept or reject it. On other trials it will be the same, except you will be responding on behalf of another player. In this case you will see what player one offered player two, and you will be asked to accept or reject that offer on behalf of player two. Sometimes, you will be presented with an offer which has

been randomly generated by a computer, and asked whether you want to accept or reject it. Sometimes you will also be asked to play as player one, and make an offer to another player. The total amount of money being split will not always be the same. It ranges from around £1 to approximately £100.

When you have completed the whole study, you will receive a proportion (1%) of the money earned based on the decisions you have made on your own behalf.

Appendix C Full list of offers in the Ultimatum Game version used in the MDMA study

Table B-1: Full list of UG offers presented in the MDMA study. Ordered by condition and then percentage of the total stake. Shading reflects unfair (10-20%), fair (45-50%), and hyper-fair (80-90%) offers. FP: first person; TP: third-party; GS: game server

Offer from…	% of total stake	Total stake	Utility
Run one			
FP	10	30	Low
FP	10.94	32	Low
FP	11.96	46	High
FP	13.04	11.5	Low
FP	13.05	38.3	High
FP	17.11	38	High
FP	20	5	Low
FP	20	37.5	High
FP	46.15	6.5	Low
FP	46.67	7.5	Low
FP	47.06	8.5	Low
FP	47.62	10.5	High
FP	48.15	13.5	High
FP	49.18	12.2	High
FP	50	2	Low
FP	50	3	Low
FP	80	2.5	Low
FP	81.08	3.7	Low
FP	82.35	8.5	High
FP	84.62	6.5	High
FP	86.36	11	High
FP	86.67	7.5	High
FP	90	5	Low
FP	90.91	1.1	Low

TP	11.97	58.5	High
TP	13.05	38.3	High
TP	13.16	19	Low
TP	14.04	28.5	Low
TP	17.91	33.5	High
TP	19.15	23.5	Low
TP	20	37.5	High
TP	20	5	Low
TP	46.67	7.5	Low
TP	47.37	9.5	Low
TP	47.62	10.5	High
TP	48.15	13.5	High
TP	50	19	High
TP	50	15	High
TP	50	3	Low
TP	50	2	Low
TP	80	5	Low
TP	82.35	8.5	High
TP	83.33	3	Low
TP	83.33	6	High
TP	85.71	7	High
TP	88.24	1.7	Low
TP	88.89	9	High
TP	90.91	1.1	Low
GS	10	30	Low
GS	11.97	58.5	High
GS	13.04	11.5	Low
GS	13.05	38.3	High
GS	14.04	28.5	Low
GS	17.02	47	High
GS	17.91	33.5	High
GS	20	5	Low
GS	46.67	7.5	Low
GS	47.06	8.5	Low
GS	47.62	10.5	High
GS	49.02	5.1	Low
GS	49.18	12.2	High
GS	50	16	High
GS	50	19	High
GS	50	2	Low
GS	80	5	Low
GS	80	2.5	Low
GS	83.33	6	High
GS	84.62	6.5	High

GS	88.24	8.5	High
GS	88.89	9	High
GS	90	5	Low
GS	90.91	1.1	Low
Run two			
FP	11.97	58.5	High
FP	13.16	19	Low
FP	14.04	28.5	Low
FP	17.02	47	High
FP	17.91	33.5	High
FP	17.92	53	High
FP	18.35	10.9	Low
FP	19.15	23.5	Low
FP	44.44	4.5	Low
FP	47.37	9.5	Low
FP	47.83	11.5	High
FP	48.28	14.5	High
FP	49.02	5.1	Low
FP	50	19	High
FP	50	16	High
FP	50	15	High
FP	80	5	Low
FP	83.33	6	High
FP	83.33	3	Low
FP	85.37	4.1	Low
FP	85.71	7	High
FP	88.24	8.5	High
FP	88.24	1.7	Low
FP	88.89	9	High
TP	10	30	Low
TP	10.94	32	Low
TP	11.96	46	High
TP	13.04	11.5	Low
TP	17.02	47	High
TP	17.11	38	High
TP	17.92	53	High
TP	18.35	10.9	Low
TP	44.44	4.5	Low
TP	46.15	6.5	Low
TP	47.06	8.5	Low
TP	47.83	11.5	High
TP	48.28	14.5	High
TP	49.02	5.1	Low
TP	49.18	12.2	High

TP	50	16	High
TP	80	2.5	Low
TP	81.08	3.7	Low
TP	84.62	6.5	High
TP	85.37	4.1	Low
TP	86.36	11	High
TP	86.67	7.5	High
TP	88.24	8.5	High
TP	90	5	Low
GS	10.94	32	Low
GS	11.96	46	High
GS	13.16	19	Low
GS	17.11	38	High
GS	17.92	53	High
GS	18.35	10.9	Low
GS	19.15	23.5	Low
GS	20	37.5	High
GS	44.44	4.5	Low
GS	46.15	6.5	Low
GS	47.37	9.5	Low
GS	47.83	11.5	High
GS	48.15	13.5	High
GS	48.28	14.5	High
GS	50	3	Low
GS	50	15	High
GS	81.08	3.7	Low
GS	82.35	8.5	High
GS	83.33	3	Low
GS	85.37	4.1	Low
GS	85.71	7	High
GS	86.36	11	High
GS	86.67	7.5	High
GS	88.24	1.7	Low

Appendix D Social value orientation questionnaire (Van Lange, 1999)

In this set of questions, we ask you to imagine that you have been randomly paired with another person, whom we will refer to simply as the "other." Other is someone you do not know and that you will not meet in the future. Both you and Other will be making choices by circling either the letter A, B, or C. Your own choices will produce points for yourself and Other. Likewise, Other's choice will produce points for him/her and for you. Every point has value: The more points you receive, the better for you, and the more points Other receives, the better for him/her.

Here's an example of how this task works.

	A	B	C
You Get	500	500	550
Other Gets	100	500	300

In this example, if you chose A you would receive 500 points and Other would receive 100 points; if you chose B, you would receive 500 points and Other 500; and if you chose C, you would receive 550 points and Other 300. So, you see that your choice influences both the number of points you receive and the number of points the other receives.

Before you begin making choices, keep in mind that there are no right or wrong answers – choose the option that you, for whatever reason, prefer most. Also, remember that the points have value: The more of them you accumulate, the better for you. Likewise, from the Other's point of view, the more points s/he accumulates, the better for him/her.

For each of the nine choice situations below, circle A, B or C, depending on which column you prefer most. Please proceed in the order the choices appear.

1.

	A	B	C
You Get	480	540	480
Other Gets	80	280	480

2.

	A	B	C
You Get	560	500	500
Other Gets	300	500	100

3.

	A	B	C
You Get	520	520	580
Other Gets	520	120	320

4.

	A	B	C
You Get	500	560	490
Other Gets	300	500	90

5.

	A	B	C
You Get	560	500	490
Other Gets	300	500	90

6.

	A	B	C
You Get	500	500	570
Other Gets	500	100	300

7.

	A	B	C
You Get	510	560	510
Other Gets	510	300	110

8.

	A	B	C
You Get	550	500	500
Other Gets	300	100	500

9.

	A	B	C
You Get	480	490	540
Other Gets	100	490	300

Appendix E Social reward questionnaire (Foulkes et al., 2014)

Instructions: Here is a list of statements about what you enjoy when you interact with other people. The statements refer to all people in your life, e.g. friends, partners, family, colleagues or people you have just met. Consider how well each statement relates to you and indicate your answer with a tick. NOTE: If there is something you have never experienced, imagine how much you *would* enjoy it.

	Strongly disagree	Disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Agree	Strongly agree
1. I enjoy being around people who think I am an important, exciting person							
2. I enjoy treating others fairly							
3. I enjoy making someone angry							
4. I enjoy going to parties							
5. I enjoy being nice to someone only if I gain something out of it							
6. I enjoy feeling emotionally connected to someone							
7. I enjoy it if others looks up to me							
8. I enjoy tricking someone out of something							
9. I enjoy having erotic relationships							
10. I enjoy being a member of a group/club							
11. I enjoy being around people who are impressed with who I am and what I do							
12. I enjoy letting someone else tell me what to do							
13. I enjoy having many sexual experiences							
14. I enjoy embarrassing others							
15. I enjoy many people wanting to invite me to their social events							
16. I enjoy keeping promises I make to others							
17. I enjoy seeing others get hurt							
18. I enjoy achieving recognition from others							
19. I enjoy it if someone accepts me as I am, no matter what							
20. I enjoy having an active sex life							
21. I enjoy someone else making decisions for me							
22. I enjoy making someone feel happy							
23. I enjoy following someone else's rules							

Appendix F Exploratory analyses on the UG fMRI data

To further explore the Ultimatum Game (UG) fMRI data, an additional analysis was carried out on the placebo data. First, a new first level model was defined to test for the effect of making a response, regardless of condition. To do this, the button response was modelled as an effect of interest, and a one-sample t-test carried out at the group level. There were three large clusters which incorporating occipital, cerebellar and post-central cortices. Additionally, bilateral insula, supplementary motor area (SMA), putamen and the cingulate cortex showed activation in this analysis. Figure E-1 displays these results.

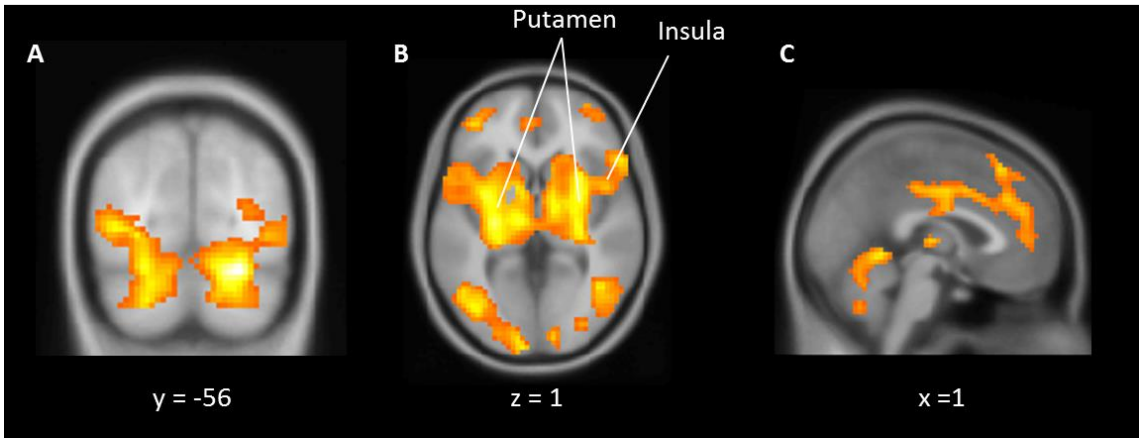

Figure E-1: Results from button press UG contrast, thresholded at FWE-corrected $p < 0.05$

Occipital, cerebellar and post-central cortices could be expected as part of the button press response, as they can be expected to be involved in the visual and motor response to the cue to make choice. Cingulate, SMA and insula are regions which were hypothesised to be involved in the cognitive response to the task. However, these regions are also part of the salience network which would be expected to be engaged when responding to an instruction to act (Fox et al., 2005; Geng et al., 2016). To establish if perhaps the activity of these regions in the current analysis could represent cognitive responses to the task, I modelled an extended offer period to include the time up until the button press of the response. At the second level I re-ran the drug-by-fairness ANOVA in the FP condition. The results were very similar as for the analysis reported in 0, with a cluster encompassing the superior temporal gyrus for the fairness contrast.

The analyses described above modelled the BOLD signal using the canonical haemodynamic response function (HRF), as is the default in SPM. Figue E-2provides a reminder of the timeline of each trial, which had four distinct periods. First, the condition was revealed (first person, third party, game server), followed by the offer, which in turn was followed by the decision period. The trial ended with a variable length spinning wheel to indicate a new partner was being found. The analyses used thus far defined the offer period as the period of interest where the onset of the HRF was modelled. To remove the assumption that, a) all the variation in BOLD signal could be captured with the canonical HRF, and b) that this could be found following the onset of the offer, the data were instead modelled with a finite impulse response (FIR).

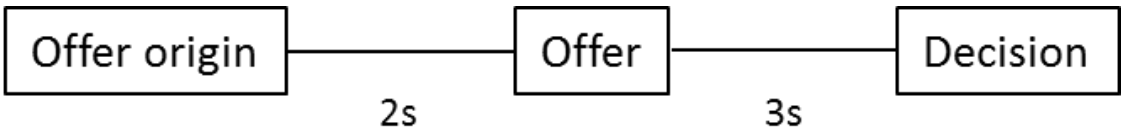

Figure E-2: Timings of the each trial in the UG task. First, where the offer originates is revealed (i.e. FP, TP or GS), then the offer is displayed for three seconds, before participants are asked to decide whether to accept or reject the offer

An FIR model imposes no assumption on the shape of the expected BOLD response (Henson et al., 2001). In this FIR analysis, eight two-second bins were defined, with the first starting at the beginning of each trial (when the condition was revealed). At the first level, first person unfair offers were contrasted with first person fair offers. At the group level, a within-subjects one-way ANOVA was carried out with an F-contrast looking for voxels with a difference in BOLD signal across conditions in any time bin.

There were three clusters were significantly difference across bins. These were in the superior frontal gyrus, middle frontal gyrus and middle occipital gyrus. Examination of the contrast values shows that these differences were driven by lower activation in the unfair compared to fair condition 14 seconds post-trial onset. This is a difference unlikely to have been captured by an HRF modelled with an onset when the offer appeared (2 seconds post-trial onset). However, it is also a difference which is difficult to explain given the trial timeline and expected task effects.

These results are discussed further in 0, Section 4.4.5.2.

Appendix G Consent form, information sheet and ethical approval for both test-retest studies

KING'S College LONDON

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: Test-retest stability of cognitive tasks

King's College Research Ethics Committee Ref: PNM/14/15-10

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes mean that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element I may be deemed ineligible for the study.

Plea

Pleas

1. **I confirm that I have read and understood the information sheet dated 27/07/14 (Version 1) for the above study. I have had the opportunity to consider the information and asked questions which have been answered satisfactorily.** ☐
2. **I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Furthermore, I understand that I will be able to withdraw my data prior to it being anonymised. A deadline for withdrawal of consent to use my data has been given to me.** ☐
3. **I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.** ☐
4. **I understand that my information may be subject to review by responsible individuals from the College for monitoring and audit purposes.** ☐
5. **I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications** ☐

6. I understand that I have been asked to participate in 1/2/3* testing sessions. ☐

7. I understand that I will/will not* be rewarded with a financial incentive. ☐

8. I agree to the researchers sharing my anonymised data for the purpose of further analysis. ☐

9. I agree that the research team may use my data for future research. ☐

10. I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. ☐

11. I understand that I must not take part if I fall under the exclusion criteria as detailed in the information sheet and explained to me by the researcher. ☐

12. I agree to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature. ☐

***delete as appropriate and initial**

_____	_____	_____
Name of Participant	**Date**	**Signature**
_____	_____	_____
Name of Researcher	**Date**	**Signature**

KING'S College LONDON

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: PNM/14/15-10

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of study: Test-retest stability of cognitive tasks

We would like to invite you to take part in a research study being conducted by the Department of Neuroimaging at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. You have been given this document to provide you with information about what the research is about, and what would be involved should you decide to take part. Please take the time to read the following information carefully before deciding whether you would like to participate. If you have any further questions, please do not hesitate to contact the project's researcher team via email or telephone: **@kcl.ac.uk, 020**********

What is the purpose of the study?

Brain imaging research often uses psychological tests which have come from other areas of research. In some cases, these tasks need to be adapted to be suitable for use in brain imaging. On other occasions, for example when an experiment is designed to investigate a drug, a participant may be required to complete a task on more than one occasion, separated by a week or more. Therefore, a researcher may need to test the adapted version of the task, or test for consistency in its results over multiple time-points before using the task in a larger research programme. The purpose of this study is to test adapted tasks for their suitability in further research.

Do I have to take part?

Participation in this study is voluntary. It is not obligatory. We will explain the nature of the study, provide you a copy of this information sheet, and address any questions you may have. If you decide to participate, we will ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving any reason. If you wish to withdraw any data already collected, this will need to be done before the data is anonymised, as after this point, your specific data is not identifiable, even to the researchers. This will typically be one month after your final visit.

What will happen to me if I take part?

The study will involve a number of visits to the Centre for Neuroimaging Sciences. The researchers will inform you of the exact number of visits for the specific study you are taking part in. Each visit will last no more than an hour and a half. At each session you will be asked to complete some tasks. The tasks will vary depending on the specific study you are taking part in, but will typically involve being presented with a stimuli (visual, auditory or tactile) and will require a response, either verbal or written, or via a button-press or joystick. The specific tasks you will be participating in will be explained in detail and you will have ample opportunity to ask questions before deciding whether to take part.

At the start of each visit, you will be briefed with full details of the tasks, and will be given an opportunity to carry out a small practice session to ensure you are comfortable with the instructions.

Incentives

Some tasks will involve a financial reward. The researchers will inform you of any financial incentives for participation in this study.

What are the possible risks of taking part?

We do not foresee any risks of taking part in this study.

What are the possible benefits of taking part?

You will not directly benefit by taking part in this research beyond any financial incentives as outlined above.

Will my taking part be kept confidential?

All personal information will be kept in a secure location at the Institute of Psychiatry, Psychology & Neuroscience. Your data will be anonymised prior to analysis, so it will not be traceable to you.

How is the project being funded?

There is no specific funding for this project, which is supported by the Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience.

What will happen to the results of the study?

The results of this study will be used to validate or improve tasks designed for neuroimaging research. In some cases the results will be disseminated at meetings at the Institute of Psychiatry, Psychology & Neuroscience, academic conferences, or published in academic journals. You will not be identified in any report of publication that results from this study.

Who should I contact for further information?

If you have any questions or require more information about this study, please contact me using the following contact details:

Dr. Mitul Mehta, Department of Neuroimaging (PO89), Institute of Psychiatry, Psychology & Neuroscience, King's College London SE5 8AF. Tel: 02032283053. Email: Mitul.mehta@kcl.ac.uk

What if I have further questions, or if something goes wrong?

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact King's College London using the details below for further advice and information:

Dr. Mitul Mehta, Department of Neuroimaging (PO89), Institute of Psychiatry, Psychology & Neuroscience, King's College London SE5 8AF. Tel: 02032283053. Email: Mitul.mehta@kcl.ac.uk

Thank you for reading this information sheet and for considering taking part in this research.

Dr Mithul Mehta
Centre for Neuroimaging Sciences (P089)
Institute of Psychiatry
King's College London
London SE5 8AF

18 September 2014

Dear Mithul,

PNM/14/15-10 Test-retest stability of cognitive tasks

Review Outcome: Full Approval

Thank you for submitting your application for ethical approval. This was reviewed by the PNM RESC on 16 September 2014. As a result, the Committee has granted full ethical approval for your study.

Provisos
Your approval is based on the following provisos being met:

1. Section 4: Please inform the Research Ethics Office of any significant changes to the study.
2. Section 7.2 and Information Sheet: The Committee recommends that you specify a standard deadline for withdrawal of participant data. This might be, for example, one week after data-collection.
3. Section 7.3: The Committee recommends that participants subject to any level of deception are appropriately debriefed.
4. Information Sheet:
    I. Please remove inapplicable template text from the sheet.
    II. Please replace any remaining references to the Institute of Psychiatry (specifically in the 1st paragraph) with Institute of Psychiatry, Psychology & Neuroscience

You are not required to provide evidence to the Committee that these provisos have been met, but your ethical approval is only valid if these changes are made. You must not commence your research until these provisos have been met.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information ethical approval is granted until 18 September 2017. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will

not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results.
For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records.
Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx)
We wish you every success with this work.

Yours sincerely,

James Patterson - Senior Research Ethics Officer

For and on behalf of

Professor Gareth Barker, Chairman

Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM RESC)

Appendix H Consent form, information sheet and ethical approval for psilocybin study

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: MICA: SRC inhibitors as potential antipsychotics: human testing with psilocybin

King's College Research Ethics Committee Ref: PNM 14/15 - 11

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes mean that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element I may be deemed ineligible for the study.

Plea ☐

Pleas

1. **I confirm that I have read and understood the information sheet dated V3.1 – 29/02/2016 for the above study. I have had the opportunity to consider the information and asked questions which have been answered satisfactorily.** ☐
2. **I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to 01/03/16** ☐
3. **I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.** ☐
4. **I understand that my information may be subject to review by responsible individuals from the College for monitoring and audit purposes.** ☐
5. **I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications** ☐

6. I understand that relevant sections of my data may be looked at by individuals from Imperial College and Kings College London. My personal data will be stored securely on University computers. All data obtained from my involvement in the study will be anonymised. I give my permission for this. ☐

7. I agree that my data/sample(s) can be transferred to other researchers for purposes connected with my participation in this study but that this will be anonymised. This data will be published in scientific journals and presented at conferences or meetings. ☐

8. I understand and agree that the MRI brain scan is not a diagnostic procedure. Should there be any concerns with what is found however, I consent to my scans being forwarded to the appropriate specialist for review and reporting. I further consent to the results of this report being disclosed to my General Practitioner and the research team. ☐

9. I consent to plasma from my blood being anonymously stored for analysis. ☐

10. I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would/would not be identifiable in any report). ☐

11. I agree to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature. You are not obliged to participate in any future research. ☐

12. I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. ☐

13. I understand that I must not take part if I fall under the exclusion criteria as detailed in the information sheet and explained to me by the researcher. ☐

14. I agree that my GP may be contacted, and the research team informed, if any unexpected results are found in relation to my health. ☐

_____	_____	_____
Name of Participant	**Date**	**Signature**
_____	_____	_____
Name of Researcher	**Date**	**Signature**

Institute of Psychiatry

at The Maudsley

KING'S College LONDON

University of London

INFORMATION SHEET FOR HEALTHY VOLUNTEERS

STUDY TITLE

MICA: SRC inhibitors as potential antipsychotics: human testing with psilocybin

A study conducted by the Centre for Neuroimaging Sciences at the Institute of Psychiatry, Psychology & Neuroscience, King's College London and sponsored by Imperial College. One of the drugs used in this study is being supplied in kind by AstraZeneca, a pharmaceutical company.

Principal Contact for general queries or in the event of adverse effects:

Dr Mitul Mehta
Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF
Telephone: 020 3228 3053/3058

We would like to invite you to take part in a research study at the Centre for Neuroimaging Sciences. Before deciding to take part it is important to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. You may talk to others about the study if you wish. The information is separated into two parts. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask if anything is unclear or if you would like more information. Take time to decide whether or not you wish to take part. If you do decide to take part, you will be given a copy of this document to take home with you. Please contact Anthony Gabay for further details on taking part: anthony.a.gabay@kcl.ac.uk / 07444321618

PART I

Purpose of the research

Brain imaging is currently used for a number of reasons including understanding where in the brain medicines act. The purpose of this study is to use brain imaging to test a mechanism by which a novel drug has effects in the brain. In order to achieve this we will use an existing drug, psilocybin (an active component of Magic Mushrooms) to see whether it will activate particular regions of your brain. This is an established model for looking at features such as hallucinations.that occur in psychiatric illnesses. We plan to assess the sensitivity of different brain imaging techniques to psilocybin and test the reversal of psilocybin's effects with a novel, experimental drug called saracatinib. This drug has previously been used in cancer research. We are doing this study to help us determine how useful these brain imaging methods may be for assessing the effects of future medicines on brain function in patients.

Do I have to take part?

Participation in the study is voluntary. It is not obligatory. We will describe the study to you, go through this information sheet and provide a copy for you to keep. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving any reason. If you do decide to withdraw from the study we will ask you if you also wish to withdraw your data collected to date, in which case this will need to be done before it is anonymised. This is planned for August 15th 2015.

What is involved?

The study will involve three separate visits to the Centre for Neuroimaging Sciences. The first will last about 2-3 hours and the other two will last about 8 hours each. Each visit will be separated by at least one week. Your involvement in this study will take between 4 and 8 weeks (depending on your availability and the sessions available at the research centre). The overall study will be on-going for approximately 12 months. We aim to have 24 volunteers complete the study.

About the medication:
Psilocybin is a short-acting psychedelic ('mind-manifesting') or hallucinogenic drug, which works by acting on the serotonin system. Serotonin is a chemical that naturally exists in the brain, low levels of which have been associated with depression. All volunteers will receive the psilocybin infusion. Information on safety and side effects is given below.

Saracatanib is an experimental medication which has been used in clinical research to investigate its anti-cancer properties. It has been shown to block a particular biochemical pathway in living cells in the body (a tyrosine kinase pathway). This same pathway is considered to be activated by psilocybin and is responsible for its characteristic psychological effects, some of which appear to transiently mimic those seen in schizophrenia. If this pathway can be blocked by saracatinib and result in the reversal of psilocybin's effects, this may offer an additional or alternative means by which we can help those patients suffering from schizophrenia. Information on safety and side effects is given below.

The two drug combinations that all patients will receive is

1. oral placebo and psilocybin infusion
2. oral saracatanib and psilocybin infusion

You will not know which combination of treatments you receive at each visit. Neither you nor the investigators will know what you have taken on each day, although we can find out quickly if needed in the case of an emergency.

First Visit: Screening Visit (2-3hours)

Physical examination:
The first visit is a screening visit. The study will be explained to you and you will be asked to sign the consent form. A copy of this form will be given to you to keep. The screening visit will include answering questions about your health, a physical examination, checking your blood pressure and pulse rate, taking a recording of your heart called an ECG (electrocardiogram) and measuring your weight. Samples of your blood and urine will also be taken which will be tested in the laboratory for any drugs of abuse. We will also test your breath for alcohol. These tests are important to gain an understanding of your state of health and confirm that your body will handle the study medication we give you in a normal manner. The samples we collect from you will only be used for the purposes described and will not be stored.

Mental health status and scanning procedures:
On the screening visit we will also request that you take part in a structured clinical interview, which will include questions about your mental health, and complete some subjective questionnaires about your mood. The purpose is to ensure all volunteers are suitable for the study.

The study will be using a magnetic field to help generate pictures of your brain, therefore you must not have a scan if you have received metal-associated injuries to your eyes, had metallic objects (including clips) inserted into your body during an operation, or if you have received a gun-shot injury or have a heart pace maker. The study physician will go through a list of possible risks with you at screening as will the person conducting the scan before you go into the scanner. You will also be given the opportunity to lie in a mock scanner at the Centre for Neuroimaging Sciences before lying in the real scanner. This will help you become accustomed to the scanning environment.

Computer tasks:
If you take part in the study you will be asked to complete some tasks on the computer. During screening there will be a practice session of these tasks in which you will receive instructions on what you will be asked to do while you are in the scanner. You will be asked to look at a computer screen and move a joystick in response to certain images.

These screening assessments, together with specific questions we will ask, will confirm your eligibility for participation in the study.

<u>Second and Third Visits: Study days (8hours each)</u>

If you are eligible to participate in the study we will invite you to take part in two subsequent scanning visits on two separate occasions at least one week apart. We will arrange these dates so that they are convenient for you. Each of these two study visits will include identical study assessments and procedures. Only the oral drugs that you receive will differ.

On each visit we will first give you a brief interview to confirm that you are still suitable to take part, explain again the study procedures, conduct a brief physical examination, test your urine for drugs of abuse and check the alcohol levels in your breath. If these are all normal we will continue with the visit.

On each scanning visit, an hour after arriving, you will receive a single dose of one of the following tablets – placebo (inert or dummy substance) or saracatinib. Neither you nor the investigators will know which of these you have been given on each day since it is decided by a random code. We'll also put a cannula (small plastic tube) into one of the veins in your arm. This may cause slight discomfort at the insertion site and occasionally bruising.

Approximately 4 hours after the tablet we will give you psilocybin, which will be delivered directly into the blood via the cannula by a programmable intravenous infusion pump. The pump controls the rate at which you will receive psilocybin to ensure everyone receives the same amount of drug at the same rate. We will plan the infusion to delivery approximately 2mg psilocybin over 1-2minutes.

Scanning Procedure:
Scanning will take place before and after you have been given the psilocybin dose. The scans will take place approximately four hours after giving you the oral tablet of placebo or saracatinib. In this time period you will be provided with something to eat and you will also be asked to complete some brief questionnaires which assess your subjective feelings (including mood, sensations, and alertness).

Each scanning session will consist of two parts, in each part you will undergo the same procedures and be asked to complete the same computer tasks. In the first part, which will last approximately one hour, we will collect pictures (scans) of your head while you are resting and whilst you are performing a computer task which will entail fixing your gaze onto a computer-generated pattern of dots on a screen. You will not be given any psilocybin during this first part. For the second part we will scan you during the psilocybin infusion and continue to scan for about 30 minutes. We will collect pictures of your head again, while you are alternately resting and again performing the task. The total time you will be in the scanner will be about 90 minutes. We will also ask you to provide us with a score that denotes the intensity of the subjective experience whilst under the influence of psilocybin. After the scanning we will ask you to perform some computerised games to test your ability to recognise emotions and make simple decisions. These games will last about 30minutes and we will show you how they work on your screening visit.

What is scanning?
We use a very modern method of scanning known as Magnetic Resonance Imaging (MRI). This technique is commonly used to diagnose a number of diseases, but in this case it has been adapted to take images of which parts of your brain are active when you at rest or performing a task. When a part of your brain is more active, more blood flows to that region and this change is captured on the images that we take. We will make a map of which parts of your brain has more blood flow than others.

In order for us to take pictures of your brain, you will have to lie as still as possible in the MRI scanner. The scanner consists of a powerful magnet, but you will not feel any force or special sensation inside a magnetic field because your body is insensitive to it. Because of the magnetic field, you must not have a scan if you have received metal injuries to your eyes, had metallic objects (including clips) inserted into your body during an operation, or if you have received a gun-shot injury or have a heart pace maker. The radiographer will go through a list of possible risks with you before you go into the scanner. Please note that MRI scans do not involve any form of ionising radiation (X-rays), but the scanner itself can be quite claustrophobic; therefore please inform us if you have a fear of enclosed spaces.

All the time you are in the scanner there will be a microphone switched on so you can talk to us. We will talk to you regularly to explain what will happen next. Some people find the machine a little noisy, but the headphones we provide allow adequate noise protection for most people.

During each study visit we will take 5 blood samples. These will be used to measure the levels of psilocybin and saracitinib in your body. One of these samples will be collected while you are lying in the scanner. These samples will either be collected by a simple needle into a vein or through the cannula in your arm (described above on page 3). The samples we collect from you will only be used for the purposes described and will not be stored. While you are in the scanner we will also monitor your heart rate and respiration rate. At intervals throughout the day we will also check your blood pressure and heart rate outside the scanner while you are lying down and again while you are standing up, and ask you to rate how you are feeling using some questionnaires. If you feel unwell for what-ever reason during the course of the day you should let one of the study team know.

Before and after your scan

If you decide to take part in this research study we ask that you visit the Centre for Neuroimaging Sciences on 3 separate occasions, one for screening and two study visits. Before each visit we ask that you:

- do not drink alcohol, take products containing caffeine or engage in strenuous exercise (e.g. heavy lifting, aerobics) for 24 hours

For the two study visits we ask that you also:

- eat nothing but a light breakfast (e.g. bowl of cereal, or two pieces of toast, nothing high in fat) between midnight and your arrival at the centre for neuroimaging sciences on the study days (not screening) and
- abstain from nicotine- or tobacco- containing products for at least 4 hours before arrival at the Centre

During the study day we will provide food but we do ask you to abstain from nicotine-, tobacco- or caffeine- containing products until you are discharged home. After each study day we will ask you to avoid alcohol and driving or operating heavy machinery for at least 24 hours after receiving each dose because small levels of psilocybin and saracatinib may still be present in your system.

You will need to provide us with a contact number. We will contact you the following day and again a week after your last visit to ensure that you are well and not experiencing any untoward effects. If necessary a physician will be available to review you in person at the study centre. We will provide you with contact numbers for the research team should you want to get in touch with us.

If you fall ill or need to take any medication through the course of the study you should notify the researcher as soon as possible.

Importantly, if you have private health insurance you should contact the company to inform them that you are taking part in a research study to ensure it does not affect your cover.

Will I experience any side effects?

Taking blood or inserting the cannula are well-tolerated procedures, although you may experience some minor discomfort, minimal bleeding or bruising in your arm.

Psilocybin is referred to as a psychedelic (meaning ‘mind-manifesting’) or hallucinogenic drug and is the active ingredient in magic mushrooms. You should be aware that these mushrooms are used socially and their consumption is against the law. Psilocybin can affect your blood pressure and heart-rate so you will not be included in the study if you have a history of high blood pressure or other heart problems. When on the drug you may feel your heart beating faster. Psilocybin can cause strange and unusual experiences (such as changes in the way things look e.g. the size and shape of things can appear distorted, walls may appear to move, shapes and colours may be seen on surfaces the room may appear to get bigger or brighter and time may appear to pass more slowly), which you will be familiar with since you have used psychedelics before. However since we will be administering psilocybin intravenously, the effects will be much more short-lived when compared to consuming magic mushrooms orally. Importantly the doses to be used in this study have been used in our studies previously with healthy volunteers and are well-tolerated. Our group has much experience working with psilocybin and have administered it to over 50 healthy volunteers. Anxiety is a rare side-effect that usually responds well to support and reassurance. Should you find these experiences unpleasant and frightening the scanning can be stopped immediately and any strange experiences should fade over the next hour – during this time you will be constantly monitored. A qualified physician will be present throughout the study periods and will examine you before you leave for the day. We will arrange for a taxi to take you home. In the unlikely event that you are unfit to leave the imaging centre you will be admitted to The Maudsley Hospital for overnight monitoring.

Saracatinib is an experimental drug, has only been used in clinical research to date and is therefore not licensed to treat any health condition presently. So far saracatinib has been given to over 50 healthy volunteers and the most likely side-effects are headache, diarrhoea, nausea and vomiting. Some volunteers experience a flu-like illness characterised by feeling hot, muscle aches and tiredness.

If you do experience any side effects please contact Dr. Mitul Mehta on 0203 228 3084/3053 or the study physician on 07444321618 immediately.

Will I benefit from my participation?

We do not expect that you will draw any specific personal benefit apart from a payment of £20 per hour to compensate for your time, which if you complete the study will amount to £350. If we decide that you are not suitable during the screening session we will pay you £30 for your time. Travel expenses will also be reimbursed.

What do I do if I want to withdraw from the study?

From our previous experience in studies of this type we do not anticipate that you will have any problems. However if you do, we want to assure you that you are free to withdraw from the study at any time. You will not be required to give us any reasons for withdrawal from the study but please inform us as soon as possible if you wish to do so. If you do decide to withdraw from the study we will ask you if you also wish to withdraw your data collected to date.

Will my participation be kept confidential?

You will be identified in our computers by a number instead of your name. All records obtained while you are in this study, including related health records, will remain strictly confidential at all times. An exception is disclosure of information that indicates you are at serious harm to yourself or others, in which case your GP and a psychiatrist may be informed. A copy of this 'Information Sheet' and of the signed 'Consent Form' will be given to you to keep. A copy of your consent may be made available to others working on the study at the Institute of Psychiatry, Psychology & Neuroscience, King's College London and Imperial College, the Independent Ethics Committee members. More information on confidentiality is given in Part II of this information sheet.

If you have any questions about matters related to the study please contact Dr. Mitul Mehta on 020 3228 3058/3053.

PART II

What if relevant new information becomes available?

Sometimes we get new information about medicines being used in research. If this happens, a member of the research team will tell you and discuss whether you should continue in the study. If you decide to continue in the study, he/she may ask you to sign an updated consent form. If the study is stopped for any other reason, we will tell you and explain the reasons why this has occurred.

Although unlikely, it is possible that whilst performing normal medical checks we may identify a significant abnormality that you didn't realise you had. If this occurs, a study doctor will discuss the finding with you and we will inform your GP. Imperial College (the Sponsor) may stop the study or your participation in the study at any time, for any reason,

without your consent. This may be due to an adverse reaction or other factors that relate to your safety or well-being. A full explanation will be given to you should this be necessary. MRI scans will be reviewed by a specialist and any significant abnormalities will be reported to your GP and the study investigators.

What will happen if I don't want to carry on with the study?

If you withdraw from the study we will retain and continue to use any data collected before such withdrawal of consent unless you request that you do not want us to use any data collected from you.

What if there is a problem?

While we do not expect you to suffer any health problems by taking part in this study, Imperial College, the study's sponsor, may compensate anyone whose health suffers as a result of participation. You do not have to prove it was anyone's fault; if the health problem arose because of your participation in this study, you will be compensated.

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact Imperial College London for further advice at: AHSC Joint Compliance Office, Imperial College, 510C, 5th Floor, Charing Cross Hospital W6 8RF*** OR King's College London using the details below for further advice and information: The Chair, Psychiatry, Nursing and Midwifery (PNM) Research Ethics Subcommittee, rec@kcl.ac.uk

Contraception

There is no information about the effect of saracatinib or psilocybin on the development of the foetus in humans or on the risk associated with your partner being exposed to saracatinib or psilocybin by the drug being passed on through your ejaculate. Therefore, it is important that your partner is not exposed to the study drugs, and does not become pregnant during the study and for a total period of three months after the receiving the last dose of the study drug.

You must inform the study team or the sponsor if your partner becomes pregnant within three months of you receiving the last dose of study drug. For the sake of safety it is important to follow-up on any such pregnancies.

As a precaution, you should use an effective means of contraception (condom and spermicide)

(irrespective of whether your female partner is sterile or not) during the time interval between taking the first dose and three months following the last dose. In addition, your female partner must use another form of effective contraception e.g. intra-uterine device (IUD; "coil"), barrier methods (e.g. condom or occlusive cap [diaphragm or cervical vault/caps] used with spermicidal gel, foam, cream, film or suppository), or use of oral, injected, or implanted hormonal methods of contraception.

If your partner is already pregnant before your study admission, you should still use condoms

or another barrier contraceptive between taking the first dose of study drug and for 3 months after. You should not donate sperm for 3 months.

Will my taking part in this study be kept confidential?

All information obtained during the study, as well as related health records, will remain strictly confidential at all times. However, these may need to be made available to others

working at the Institute of Psychiatry, Psychology & Neuroscience, King's College London or Imperial College's behalf, the Ethics Committee members.

By signing the consent form you agree to this access for the current study and any further research that may be done. However, the Institute of Psychiatry and Imperial College will take steps to protect your personal information and will not include your name on any sponsor forms, reports, publications, or in any future disclosures. If you withdraw from the study, we will no longer collect your personal information, but we may need to continue to use information already collected. The study information collected may be sent to other locations outside of the UK, but you will not be referred to by name or identified in any report or publication nor could the information be traced back to you. This will be for healthcare and/or medical research purposes only. Your data will only be shared with countries where data protection laws are comparable to those in the UK. However, the Institute of Psychiatry, *Psychology & Neuroscience, King's College London* and Imperial College maintain high standards of confidentiality and protection.

Under the data protection laws Imperial College is the controller of your personal data. Imperial College will take steps to ensure your personal data is protected.

You may withdraw your permission at any time by providing written notice to the study team. The study doctor and staff would then no longer use or share your personal health information in connection with this study; unless it is essential to ensure that the study is scientifically reliable. However, we would still use study data that was collected before you withdrew your permission. In addition, you would no longer be able to participate in the study.

If you agree to take part in the study we may use the data collected in the following ways:

1. Your study data, either alone or combined with data from other studies, may be shared with collaborators from other countries in order to address scientific questions. Any data shared will be anonymized and will remain under the control of the sponsor.
2. Study data that does not identify you may be published in medical journals or shared with others as part of scientific discussions.

You have the right to see and copy your personal health information related to the research study for as long as the study doctor or research institution holds this information. However, to ensure the scientific integrity of the study, you will not be able to review some of your personal health information related to the study, until after the study has been completed.

YOUR RIGHTS UNDER ANY APPLICABLE DATA PROTECTION LAWS ARE NOT AFFECTED

What will happen to any samples I give?

We will ask you to provide a number of urine and blood samples for this study. During the screening visit we will take up to 20mL (about 3.5 teaspoons) of blood from a vein in your arm and a urine sample. During subsequent visits we will take no more than 48mL (about 8 teaspoons) of blood across all time points to measure the drug levels in your body. Overall we will not take more than 116mL (about 19 teaspoons) of blood over the course of the three visits of the study. Once the samples have been analysed, they will be destroyed.

What will happen to the results of the research study?

The results of this research will be published as scientific reports and maybe presented at meetings within the Institute of Psychiatry, Psychology & Neuroscience, King's College London or Imperial College or at international scientific meetings. You will not be identified in any report or publication that results from this study.

Who is organising and funding the research?

The research is being organized as a collaborative study between the Institute of Psychiatry, Psychology & Neuroscience, King's College London and Imperial College, who is sponsoring the study. The study is funded by the Medical Research Council, UK. One of the study drugs is being provided under a collaboration agreement by AstraZeneca Pharmaceuticals. The researchers involved in conducting this study do not receive any financial incentives for including you in this study and do not benefit financially from this study.

Who has reviewed the study?

This research study has been looked at by two independent groups of people. The first is the Medical Research Council (UK) who determined the scientific merits of this study. The second is a Research Ethics Committee, who reviewed the study and documentation to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the Psychiatry, Nursing and Midwifery (PNM) Research Ethics Committee at King's College London.

If you have any questions about matters related to the study please contact Dr. Mitul Mehta on 020 3228 3053/3058.

Dr Mitul Mehta
Centre for Neuroimaging Sciences (P089)
Institute of Psychiatry, Psychology and Nursing
King's College London
London SE5 8AF

06 January 2015

Dear Mitul,

PNM/14/15-11 MICA: SRC inhibitors as potential antipsychotics: human testing with psilocybin

Review Outcome: Full Approval

Thank you for sending in the amendments/clarifications requested to the above project. I am pleased to inform you that these meet the requirements of the PNM RESC and therefore that full approval is now granted.
Provisos

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information ethical approval is granted until 06 January 2016. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results.
For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records.
Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx)
We wish you every success with this work.

Yours sincerely,

James Patterson – Senior Research Ethics Officer

Appendix I Consent form, information sheet and ethical approval for MDMA study

KING'S College LONDON

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: The psychopharmacology of social and emotional cognition

King's College Research Ethics Committee Ref: PNM 14/15 - 32

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes mean that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element I may be deemed ineligible for the study.	**Please tick** ☐

	Please tick
1. ***I confirm that I have read and understood the information sheet dated Version 1 – 14/10/2014 for the above study. I have had the opportunity to consider the information and asked questions which have been answered satisfactorily.**	☐
2. ***I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to the point at which data collection ceases (approximately October 2016)**	☐
3. ***I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.**	☐
4. ***I understand that my information may be subject to review by responsible individuals from the College for monitoring and audit purposes.**	☐
5. **I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications**	☐

6. I agree that my data/sample(s) can be transferred to other researchers for purposes connected with my participation in this study but that this will be anonymised. This data will be published in scientific journals and presented at conferences or meetings. ☐

7. I understand and agree that the MRI brain scan is not a diagnostic procedure. Should there be any concerns with what is found however, I consent to my scans being forwarded to the appropriate specialist for review and reporting. I further consent to the results of this report being disclosed to my General Practitioner and the research team. ☐

8. I agree to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature. ☐

9. I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would not be identifiable in any report). ☐

10. I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. ☐

11. I understand that I must not take part if I fall under the exclusion criteria as detailed in the information sheet and explained to me by the researcher. ☐

12. I agree that my GP may be contacted if any unexpected results are found in relation to my health. ☐

_____	_____	_____
Name of Participant	**Date**	**Signature**

_____	_____	_____
Name of Researcher	**Date**	**Signature**

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: ***PNM/14/15-32***

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of study: The psychopharmacology of social and emotional processing

We would like to invite you to take part in a research study being conducted by the Department of Neuroimaging at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. You have been given this document to provide you with information about what the research is about, and what would be involved should you decide to take part. Please take the time to read the following information carefully before deciding whether you would like to participate. If you have any further questions, please do not hesitate to contact the project's researcher team via email or telephone: anthony.a.gabay@kcl.ac.uk, 020 3228 3095

What is the purpose of the study?

The processing of social and emotional information is an integral part of everyday human experience. They are processes which are disrupted in a number of psychiatric disorders, and urgent research is needed to improve the quality of life of patients experiencing these disorders. In order to develop treatments it is vital to first fully understand how social and emotional information is processed in the healthy brain, by identifying the neurochemical mechanisms responsible. The purpose of this study is to establish, using functional brain imaging, the mechanisms by which a recreational drug known to affect these processes, alters social and emotional processing.

Why have I been invited to take part?

You have been invited to take part in this study because you have expressed an interest after seeing an advert or hearing about it from a friend.

Do I have to take part?

Participation in this study is completely voluntary. We will explain the nature of the study, provide you a copy of this information sheet, and address any questions you may have. If you decide to participate, we will ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving any reason. We will ask if you wish us to destroy any data already collected. Should this be the case, it will need to be done before the data is anonymised, as after this point, your specific data is not identifiable, even to the researchers. This will be in October 2016.

What will happen to me if I take part?

The study will involve three visits to the Centre of Neuroimaging Sciences. The first visit will be a screening visit and will last about 2.5 hours and the other two (study days) will last about five hours each. Each visit will be separated by at least a week. Further information about each visit is provided below. The schedule for both study days will be identical, with only the drug you are given being different. You will either be given an inactive placebo, or 100mg MDMA (3,4-methylenedioxy-N-methylamphetamine).

MDMA is a compound which has been used recreationally for its euphoric effects for many years. It is the main ingredient in what is commonly known as ecstasy. It was first synthesised in the early 20th century, and was widely investigated in the mid-20th century for its possible psychotherapeutic effects. Recently MDMA has been studied in clinical trials for post-traumatic stress disorder and in studies similar to this one - to understand its effects on brain function. MDMA produces its subjective effects by acting on the brain's serotonin system. Further detail about safety and sides effects is given below.

First visit: Screening visit (approximately 2 hours)

Physical and mental health screening:
The first visit is a screening visit. The study will be explained to you and you will be asked to sign the consent form. A copy of this form will be given to you to keep. The screening visit will include answering questions about your health, a physical examination, checking your blood pressure and pulse rate, taking a recording of your heart called an ECG (electrocardiogram) and measuring your weight. Samples of your blood (12ml, approximately two teaspoons) and urine will also be taken which will be tested in the laboratory for any drugs of abuse. We will also test your breath for alcohol. These tests are important to gain an understanding of your state of health and confirm that your body will handle the study medication we give you in a normal manner. The samples we collect from you will only be used for the purposes described and will not be stored.

On the screening visit we will also request that you take part in a structured clinical interview, which will include questions about your mental health, and complete some questionnaires. We will also ask you questions about your lifetime use of illegal drugs. This information will be kept confidential and anonymised. The purpose is to ensure that all volunteers are suitable for the study.

The study will be using a magnetic field to help generate pictures of your brain, therefore you must not have a scan if you have received metal-associated injuries to your eyes, had metallic objects (including clips) inserted into your body during an operation, or if you have received a gun-shot injury or have a heart pacemaker. The study physician will go through a list of possible risks with you at screening as will the person conducting the scan before you go into the scanner. You will also be given the opportunity to lie in a mock scanner at the Centre for Neuroimaging Sciences before lying in the real scanner. This will help you become accustomed to the scanning environment.

During this visit you will also be introduced to all of the tasks and questionnaires used on the study day, and you will be given an opportunity to practice them.

Computer tasks:

If you take part in the study you will be asked to complete some tasks on a computer. During the screening visit you will be introduced to these tasks, and given an opportunity to practice them. You will be asked to look at a computer screen and make button-press responses to various stimuli.

These screening assessments, together with specific questions we will ask, will confirm your eligibility for participation in the study.

Second and Third Visits: Study days (5 hours each)

If you are eligible to take part in the study, you will be invited to two subsequent study days. These will be arranged at your convenience and will be at least one week apart. Each study day will be identical with just the drug you are given being different. You will either receive an inactive placebo or 100mg MDMA.

On each visit we will first conduct a short interview and urine drugs test to confirm that you are still able to take part. We will take a sample of your blood to determine baseline levels of the hormone oxytocin. You will then be given a capsule containing either placebo or MDMA – neither you nor the researcher will know what the capsule contains on each day. However, should the need arise, the researcher can very quickly find out what the capsule contained.

You will then be reminded of the tasks and given an opportunity to practice them. Approximately 60 minutes after taking the capsule, we will take another blood sample and you will be invited to enter the Magnetic Resonance Imaging (MRI) machine for scanning (see below for details about MRI scanning). The scanning procedure will take approximately 1 hour and a half in total. While in the scanner we will first take some structural scans. These will not require you to do anything other than lie very still. You then be asked to complete two tasks. These two tasks will involve making some simple decisions, via button presses, in the context of a simple game involving other people. These tasks will be interspersed with some 'resting state' scans, during which all you have to do is stare at a fixation point.

Once both tasks are completed, we will take you out of the scanner and we will collect a final blood sample. You will then be asked to complete a small number of questionnaires. We will then ask you to complete four further tasks, which will take about an hour and fifteen minutes in total. Two of those tasks will involve looking at images of people on a computer screen and answering questions about their emotional state. The third will involve making simple button press responses to visual stimuli. Finally, we will ask you to make some monetary offers to other players in the games you played in the scanner.

The total amount of blood taken on each study day will be 36ml (about 6 teaspoons).

About MRI scanning
We use a very modern method of scanning known as Magnetic Resonance Imaging (MRI). This technique is commonly used to diagnose a number of diseases, but in this case it has been adapted to take images of which parts of your brain are active when you at rest or performing a task. When a part of your brain is more active, more blood flows to that region and this change is captured on the images that we take. We will make a map of which parts of your brain has more blood flow than others.

In order for us to take pictures of your brain, you will have to lie as still as possible in the MRI scanner. The scanner consists of a powerful magnet, but you will not feel any

force or special sensation inside a magnetic field because your body is insensitive to it. Because of the magnetic field, you must not have a scan if you have received metal injuries to your eyes, had metallic objects (including clips) inserted into your body during an operation, or if you have received a gun-shot injury or have a heart pace maker. The radiographer will go through a list of possible risks with you before you go into the scanner. Please note that MRI scans do not involve any form of ionising radiation (X-rays), but the scanner itself can be quite claustrophobic; therefore please inform us if you have a fear of enclosed spaces.

All the time you are in the scanner there will be a microphone switched on so you can talk to us. We will talk to you regularly to explain what will happen next. Some people find the machine a little noisy, but the headphones we provide allow adequate noise protection for most people.

What are the possible benefits of taking part?

We do not expect that you will draw any specific personal benefit apart from a payment of £20 per hour to compensate for your time on the study days, and £20 for the screening session. If you complete the study this will amount to £220. In addition, you will be paid a proportion of the money you earn through the monetary tasks. Travel expenses will also be reimbursed.

If you wish to view a copy of any scientific reports resulting from this research, you may ask the researcher.

What are the possible risks of taking part?

During the screening session we will take a small amount of blood. This is a well-tolerated procedure, although you may experience some minor discomfort, minimal bleeding or bruising in your arm.

MDMA is often used as a recreational drug and has been used a number of research studies in different countries. You should be aware that its recreational use is against the law. MDMA can affect your blood pressure and heart-rate, so you will not be included in the study if you have a history of high blood pressure or other heart problems. When on the drug you may feel your heart beating faster. Some people report experiencing mild anxiety after taking MDMA. It is important to note that the dose being used in this study has been well-tolerated in a number of previous studies in healthy volunteers. We will, however, have a study doctor on hand to provide support, reassurance, and medical assistance if required. Should you find the experience distressing, the scanning can be stopped immediately, and any distressing feelings should pass within a couple of hours, during which time you will be monitored continually.

At the end of the study day a doctor will carry out a series of short assessments to ensure you are fit to leave the study centre. People sometimes report feeling ‘low’ for a few days after taking MDMA. A member of the study team will phone you two days after each of the study days to see how you are getting on. You should feel free to contact the study team if you are having distressing thoughts or feelings on 07444321618.

Sometimes the tests we perform reveal a significant abnormality. If this occurs we will inform your GP. The MRI scans will be reviewed by a specialist and any significant abnormalities will be reported to your GP and the study investigators.

Will my taking part be kept confidential?

If you choose to participate in this study you will be identified in our computers by a number instead of your name. All records obtained while you are in this study, including related health records, will remain strictly confidential at all times. An exception is disclosure of information that indicates you are at serious harm to yourself or others, in which case your GP and a psychiatrist may be informed. All participants having an MRI scan at the Department of Neuroimaging have their scans viewed by a clinical radiologist. In the event that any abnormality is found, they will inform the research team and your GP, who will get in contact with you to discuss this.

A copy of this 'Information Sheet' and of the signed 'Consent Form' will be given to you to keep. A copy of your consent form may be made available to others working on the study at the Institute of Psychiatry, Psychology & Neuroscience.

How is the project being funded?

This project is being funded by an IoPPN Excellence/MRC Postgraduate Studentship and the Department of Neuroimaging.

What will happen to the results of the study?

The results of this study will be disseminated in academic journals and conferences and will also contribute to a PhD thesis.

Who should I contact for further information?

If you have any questions or require more information about this study, please contact me using the following contact details:

Anthony Gabay
Centre of Neuroimaging Studies, PO 89 De Crespigny Park
London SE5 8AF
Tel: 02032283095 / 07444321618
Email: anthony.a.gabay@kcl.ac.uk

What if I have further questions, or if something goes wrong?

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact the Principal Investigator using the details below for further advice and information:

Dr Mitul Mehta
Centre of Neuroimaging Studies, PO 89 De Crespigny Park
London SE5 8AF
Tel: 0203 228 3084
Email: mitul.mehta@kcl.ac.uk

Thank you for reading this information sheet and for considering taking part in this research.

Anthony Gabay
Centre of Neuroimaging Sciences
Institute of Psychiatry, Psychology and Neuroscience
King's College London
PO 089
De Crespigny Park
London SE5 8AF

06 January 2015

Dear Anthony,

PNM/14/15-32 The psychopharmacology of social and emotional cognition

Review Outcome: Full Approval

Thank you for sending in the amendments/clarifications requested to the above project. I am pleased to inform you that these meet the requirements of the PNM RESC and therefore that full approval is now granted.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information ethical approval is granted until 06 January 2018. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results.
For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records.
Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx)
We wish you every success with this work.

Yours sincerely,

James Patterson – Senior Research Ethics Officer

Cc: Mitul Mehta